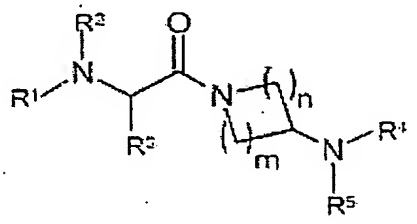
MELANOCORTIN RECEPTOR AGONISTS

TECHNICAL FIELD

The present invention relates to a compound of the following formula 1, pharmaceutically acceptable salt, hydrate, solvate, and isomer thereof effective as an agonist for melanocortin receptor.



(I)

in which

R^1, R^2, R^3, R^4, R^5, n and m are defined as described below.

BACKGROUND ART

Five subtypes of receptors have been cloned and characterized in the melanocortin family. These G-protein coupled receptors (GPCR) stimulate the cAMP signal transduction pathway in many different tissues, mediating a wide range of physiological functions. Melanocortin 1 receptor (MC1R) is mainly expressed in melanocytes, monocytes, and mast cells, to mediate pigmentation of the hair and skin and to block inflammation. MC2R is expressed in adipocytes and adrenal cells, to mediate steroidogenesis in the adrenal gland. MC3R is present in the brain, hyphothalamus, heart, gut, and placenta, and has been associated with energy homeostasis and inflammation. MC4R is uniquely expressed in the brain, and controls feeding behavior, energy homeostasis, and erectile function. MC4R knock-out mice revealed the phenotype of hyperphasia and obesity. MC5R is found in a wide range of tissues and is considered to play a role for the exocrine gland system.

With a plethora of physiological functions of melanocortin receptors, a large number of compounds have been designed and synthesized in search for potent agonists and antagonists.

Early examples are synthetic peptides and peptide analogues that have been identified on the basis of endogenous agonist such as αMSH. These peptide agonists have been used to characterize the function of these receptors. NDP-αMSH is a highly potent and nonselective agonist of MC1R, 3R, 4R and 5R, and has been reported to attenuate food intake and body weight gain in rat models. A cyclic heptapeptide MT-II is an agonist with a similar non-selective profile, and its therapeutic use has been proven in clinical trials for the treatment of erectile dysfunction. HP-228, a peptide analogue with similar affinity for all four receptors, was in clinical trials for the treatment of pain and inflammation associated with surgery.

Several small molecule agonists for the melanocortin receptors have been discovered to have significant activity in drug trials to search MC4R agonists for the treatment of obesity, sexual dysfunction or inflamation. For example, the Merck research group has discovered a series of potent and selective MC4R agonists, one of which demonstrated significant effect for augmenting erectile response in mice (*J. Med. Chem.* 2002, *45*, 4849). The Chiron research group has discovered a series of guanidine compounds as agonists that have hyphophasic activity and thus anti-obesity effect in the ob/ob mouse model (WO 02/18327). On the other hand, the Bristol-Myers Squibb group has discovered a highly potent selective MC1R agonist, which showed efficacy in an acute mouse model of inflammation (*J. Med. Chem.* 2003, *46*, 1123).

In view of the unresolved deficiencies of the various pharmaceutical compounds as discussed above, there is continuing need in the art for small molecule MCR agonists and pharmacological compositions that have improved pharmacological profiles. It is, therefore, an object of the present invention to provide novel compounds that are useful for the treatment of obesity, diabetes, sexual dysfunction, and inflammation.

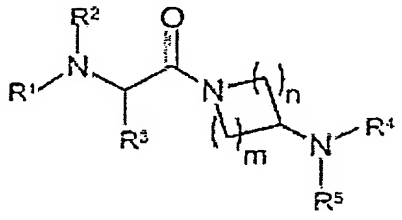
Specifically, the present invention provides a compound of formula 1 having agonistic effect against MCRs, in particular selective agonistic effect against MCR4, and pharmaceutically acceptable salt, hydrate, solvate, and isomer thereof.

Another object of the present invention is to provide a melanocortin receptor agonistic composition comprising the compound of formula 1, and pharmaceutically acceptable salt, hydrate, solvate, and isomer thereof, as active ingredients, together with pharmaceutically acceptable carrier.

In particular, the composition according to the present invention has potent effect for the prevention and treatment of diabetes, erectile dysfunction, obesity, and inflammation.

DISCLOSURE OF THE INVENTION

The present invention relates to a compound of the following formula 1, and pharmaceutically acceptable salt, hydrate, solvate, and isomer thereof.



1

in which

m and n each independently represents 1 or 2,

R^1 reperesents
hydrogen,
$-(CH_2)_p-R^6$,
$-(CH_2)_p-CO-(CH_2)_p-R^6$,
$-(CH_2)_p-CO-(CH_2)_p-CH(R^6)(R^{10})$, or
$-(CH_2)_p-SO_2-(CH_2)_p-R^6$,

wherein

p independently represent 0, 1, 2, or 3,

R^6 represents C_1-C_{10}-alkyl, C_1-C_8-alkoxy, C_3-C_8-cycloalkyl, heterocycle, aryl, heteroaryl, amino, or hydroxy, in each of which is unsubstituted or mono- or poly-substituted by one or more substituents selected from the group consisting of C_1-C_{10}-

alkyl, C_1-C_{10}-dialkyl, C_3-C_{13}-cycloalkyl, C_3-C_{13}-dicycloalkyl, C_3-C_{13}-tricycloalkyl, perhalo-C_1-C_8-alkyl, aryl, heteroaryl, heterocycle, hydroxy, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkoxy, trifluoromethoxy, aryl-C_1-C_8-alkyloxy, aryloxy, oxo, mercapto, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylsulfonyl, arylsulfonyl, C_1-C_8-alkylthio, arylthio, cyano, formyl, halogen, carbonyl, thiocarbonyl, C_3-C_8-cycloalkylcarbonyl, arylcarbonyl, ar-C_1-C_8-alkyl, ar-C_1-C_8-alkylcarbonyl, ar-C_1-C_8-alkylsulfonyl, O-carbamoyl, N-carbamoyl, O-thiocarbamoyl, N-thiocarbamoyl, carbamoyl, C_1-C_8-alkylcarbamoyl, di(C_1-C_8-alkyl)carbamoyl, O-sulfoneamido, N-sulfonamido, carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, trihalomethanesulfonyl, amino, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, and protective derivatives thereof,

R^{10} represents heterocycle, or represents amino or hydroxy, in each of which is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7,

wherein,

R^7 represents halogen, amino, C_1-C_6-alkylamino, di(C_1-C_6-alkyl)amino, hydroxy, C_1-C_8-alkoxy, trifluoromethoxy, C_1-C_6-alkylcarbonyl, carboxy, C_1-C_8-alkyl, mercapto, C_1-C_{10}-alkylthio, phenoxy, C_1-C_8-alkoxycarbonyl, arylcarbonyl, carbamoyl, C_1-C_6-alkylsulfonyl, arylsulfonyl, cyano or oxo,

R^6 and R^{10} may form 5- or 6-membered single ring together with the atoms to which they attached,

hydrogen atom in $-(CH_2)_p-$ group can be replaced by R^6,

R^2 represents

hydrogen,

C_1-C_8-alkyl which is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7,

C_3-C_7-cycloalkyl, or

$-CO-(CH_2)_p-R^6$,

R^1 and R^2 together with the atoms to which they attached, may form 4- or 8-membered

single ring or two ring which can contain heteroatom selected from the group consisting of O, S and N-(C_1-C_4-alkyl),

R^3 and R^4 each independently represents
hydrogen,
C_1-C_8-alkyl,
-$(CH_2)_p$-C_3-C_8-cycloalkyl,
-$(CH_2)_p$-C_6-C_{10}-aryl,
-$(CH_2)_p$-heteroaryl, or
-$(CH_2)_p$-heterocycle,

wherein, alkyl, cycloalkyl, heterocycle, aryl, or heteroaryl, in each of which is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7,

R^5 represents
hydrogen,
C_1-C_6-alkyl,
-$(CH_2)_p$-CO-R^8,
-$(CH_2)_p$-C(O)N(R^8)(R^9),
-$(CH_2)_p$-C(S)N(R^8)(R^9),
-$(CH_2)_p$-SO_2-N(R^8)(R^9), or
-$(CH_2)_p$-SO_2-R^8,

wherein,
R^8 and R^9 each independently represents
hydrogen,
C_1-C_8-alkyl,
C_1-C_6-alkoxy,
C_1-C_6-alkylthio,
C_3-C_7-cycloalkyl,
C_3-C_7-cycloalkenyl,
heterocycle,
aryl, or
heteroaryl,

wherein

alkyl, cycloalkyl, or aryl is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7, C_3-C_8-cycloalkyl, heterocycle, hydroxy-C_1-C_8-alkyl, halogen-C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, amino-C_1-C_8-alkyl, C_3-C_8-cycloalkyloxy, ar-C_1-C_8-alkyloxy, aryloxy, arylthio, formyl, C_1-C_8-alkylcarbamoyl, di(C_1-C_8-alkyl)carbamoyl, C_1-C_8-alkylcarbonyloxy, C_1-C_8-alkoxy-C_1-C_8-alkoxy, C_3-C_8-cycloalkylcarbonyl, ar-C_1-C_8-alkylcarbonyl, C_2-C_8-alkanoyloxy, C_3-C_8-cycloalkylcarbonyloxy, arylcarbonyloxy which is unsubstituted or substituted by halogen, ar-C_1-C_8-alkylcarbonyloxy, C_1-C_8-alkoxyimino, ar-C_1-C_8-alkylsulfonyl, and C_1-C_8-alkylsulfonyloxy,

heterocycle, cycloalkenyl, or heteroaryl is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7, and hydroxy-C_1-C_8-alkyl,

R^4 and R^5 together with the atoms to which they attached, may form 4- or 8-membered single ring or two ring which can contain heteroatom selected from the group consisting of O, S and N-(C_1-C_4-alkyl).

In the radical definitions of the compound of formula (1) according to the present invention, the term "alkyl" means straight-chain or branched hydrocarbon radical when used alone or in combination with hetroatoms such "alkyloxy."

The term "cycloalkyl" represents unsaturated aliphatic ring including cyclohexyl.

The term "aryl" represents 6- to 10- membered aromatic group including phenyl, naphthyl, etc.

The term "heteroaryl" includes 1 to 2 heteroatom(s) from the group consisting of nitrogen atom, oxygen atom, and sulfur atom, and represents aromatic 3- to 6-membered ring which can be fused with benzo or C_3-C_8-cycloalkyl. Examples of monocyclic heteroaryl are, but are not limited to, thiazole, oxazole, thiophene, furane, pyrrole, imidazole, isoxazole, pyrazole, triazole, thiadiazole, tetrazole, oxadiazole, pyridine, pyridazine, pyrimidine, pyrazine, and similar group to them. Examples of acyclic heteroaryl are, but are not limited to, indole, benzothiophene, benzofuran,

benzimidazole, benzoxazole, benzisoxazole, benzthiazole, benzthiadiazole, benztriazole, quinoline, isoquinoline, purine, furopyridine, and similar group to them.

The term "heterocycle" includes 1 to 2 heteroatom(s) from the group consisting of nitrogen atom, oxygen atom, and sulfur atom, and represents 4- to 8-membered ring which can be fused with benzo or C_3-C_8-cycloalkyl, and which is saturated or has 1 or 2 of double bond. Its examples are, but are not limited to, piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, and similar group to them.

Preferred compounds among the compounds of formula 1 above are those wherein

i) R^1 represents hydrogen, $-(CH_2)_p-R^6$, $-(CH_2)_p-CO-R^6$, $-CO-(CH_2)_p-R^6$, $-(CH_2)_p-CO-(CH_2)_p-CH(R^6)(R^{10})$, or $-SO_2-(CH_2)_p-R^6$,

R^6 represents C_1-C_{10}-alkyl, C_1-C_8-cycloalkyl, heterocycle, aryl, or heteroaryl, or represent amino or hydroxy,

hydrogen atom in $-(CH_2)_p-$ group can be replaced by R^6,

wherein

C_1-C_{10}-alkyl, C_1-C_8-cycloalkyl, heterocycle, aryl, or heteroaryl is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7,

amino or hydroxy is unsubstituted or mono- or di-substituted by the substituents selected from the group consisting of C_1-C_{10}-alkyl, ar-C_1-C_8-alkyl, C_3-C_8-cycloalkyl, C_2-C_8-alkylcarbonyl, C_3-C_8-cycloalkylcarbonyl, arylcarbonyl, ar-C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbamoyl, C_1-C_8-alkylcarbamoyl, di(C_1-C_8-alkyl)carbamoyl, C_1-C_8-alkylsulfonyl, arylsulfonyl, and ar-C_1-C_8-alkylsulfonyl,

R^{10} is defined as the above desecription,

R^6 and R^{10} may form 5- or 6-membered single ring together with the atoms to which they attached,

preferably, R^1 represents hydrogen, $-(CH_2)_p-R^6$, $-(CH_2)_p-CO-R^6$, $-CO-(CH_2)_p-R^6$ or $-(CH_2)_p-CO-(CH_2)_p-CH(R^6)(R^{10})$, ,

more preferably, R^1 represents hydrogen, $-R^6$ or $-CO-CH(R^6)(R^{10})$,

R^{10} represents heterocycle, or represents amino or hydroxy, in each of which is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7,

R^6 and R^{10} may form 5- or 6-membered single ring together with the atoms to which they attached,

ii) R^2 represents hydrogen or C_1-C_6-alkyl,

iii) R^3 represents C_1-C_8-alkyl, $-(CH_2)_p-C_3$-C_7-cycloalkyl, $-(CH_2)_p$-phenyl, or $-(CH_2)_p$-heteroaryl, in each of which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of R^7,

preferably, R^3 represents $-CH_2$-cyclohexyl or $-CH_2$-phenyl, in each of which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of halogen, cyano, hydroxy, C_1-C_8-alkoxy, trifluoromethoxy and C_1-C_4-alkyl,

more preferably, R^3 represents $-CH_2$-phenyl, in which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of chloro, bromo, cyano, hydroxy, methoxy and metyhl,

iv) R^4 represents C_1-C_8-alkyl, or represent C_3-C_8-cycloalkyl, phenyl, heteroaryl, or heterocycle, in each of which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of R^7,

preferably, R^4 represents C_3-C_8-cycloalkyl or phenyl,

more preferably, R^4 represents cyclohexyl, cylcoheptyl or cylcopentyl, in each of which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of methyl, ethyl, t-butyl, hydroxy and oxo, or represent phenyl unsubstituted or mono- to tri-substituted by substituents from the group consisting of fluoro, chloro, methoxy and methyl,

v) R^5 represents hydrogen, C_1-C_6-alkyl, $-(CH_2)_p-CO-R^8$, $-(CH_2)_p-C(O)N(R^8)(R^9)$, or $-(CH_2)_p-SO_2-R^8$,

preferably, R^5 represents $-CO-R^8$ or $-C(O)N(R^8)(R^9)$,

more preferably, R^8 and R^9 each independently represents hydrogen, methoxy, amino, C_1-C_8-alkyl, C_3-C_6-cycloalkyl, C_5-C_6-cycloalkenyl, heterocycle, or phenyl,

wherein, C_1-C_8-alkyl or C_3-C_6-cycloalkyl is unsubstituted or mono-substituted by the substituents selected from the group consisting of methyl, hydroxy, amino, C_1-C_4-alkoxy, phenoxy, benzyloxy, fluoro, phenylsulfoxy, acetyl, methoxymethylalkoxy, carboxy, formyl, methoxycarbonyl, dimethylcarbamoyl, carboxy, phenylcarbonyloxy, methoxycarbonyl, difluorophenylcarbonyloxy, dimethylphenylcarbonyloxy, cyclohexylcarbonyloxy, arylcarbonyloxy, and oxo,

C_5-C_6-cycloalkenyl represents cyclopentyl or cyclohexyl substituted by hydroxy or amino,

heterocycle or phenyl is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of hydroxy, methyl, amino, nitrobenzenesulfonyl, and oxo.

vi) R^1 represents hydrogen, $-R^6$ or $-CO-CH(R^6)(R^{10})$,

R^{10} represents heterocycle, or represents amino or hydroxy, in each of which is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of R^7,

R^6 and R^{10} may form 5- or 6-membered single ring together with the atoms to which they attached,

R^3 represents -CH_2-phenyl, in which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of chloro, bromo, cyano, hydroxy, methoxy and metyhl,

R^4 represents cyclohexyl, cylcoheptyl or cylcopentyl, in each of which is unsubstituted or mono- to tri-substituted by substituents from the group consisting of methyl, ethyl, t-butyl, hydroxy and oxo, or represent phenyl unsubstituted or mono- to tri-substituted by substituents from the group consisting of fluoro, chloro, methoxy and methyl,

R^5 represents -CO-R^8 or -C(O)N(R^8)(R^9),

R^8 and R^9 each independently represents hydrogen, methoxy, amino, C_1-C_8-alkyl, C_3-C_6-cycloalkyl, C_5-C_6-cycloalkenyl, heterocycle, or phenyl,

wherein, C_1-C_8-alkyl or C_3-C_6-cycloalkyl is unsubstituted or mono-substituted by the substituents selected from the group consisting of methyl, hydroxy, amino, C_1-C_4-alkoxy, phenoxy, benzyloxy, fluoro, phenylsulfoxy, acetyl, methoxymethylalkoxy, carboxy, formyl, methoxycarbonyl, dimethylcarbamoyl, carboxy, phenylcarbonyloxy, methoxycarbonyl, difluorophenylcarbonyloxy, dimethylphenylcarbonyloxy, cyclohexylcarbonyloxy, arylcarbonyloxy, and oxo,

C_5-C_6-cycloalkenyl represents cyclopentyl or cyclohexyl substituted by hydroxy or amino,

heterocycle or phenyl is unsubstituted or mono- or poly-substituted by the substituents selected from the group consisting of hydroxy, methyl, amino, nitrobenzenesulfonyl, and oxo.

Representative compounds of formula 1 according to the present invention include the compounds listed in the following Table 1.

Table 1

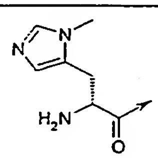
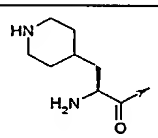
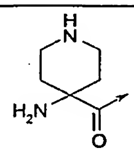
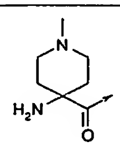
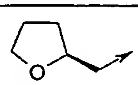
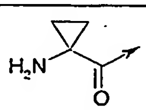
R^1	R^2	R^3	*1	n	m	R^4	*2	R^5
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_3$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)OMe
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)N(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	SO_2Me
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$CH_2C(O)OMe$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	SO_2NH_2
H	H	4-Cl-Bn	R	2	1	c-Hex	S	Gly
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$CH_2C(O)N(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	CH_2SO_2Me
H	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)C(Me)_3$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[(R)-$CH(Me)CH_2OH$]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2OH$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2)_2$-OH
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(Me)-$(CH_2OH)_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OMe$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OBn$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(-$(CH_2)_4$-)CH_2OH
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2)_3O$-(2,4-diMe-Ph)
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)CH_2OA$c
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C[-$(CH_2)_2$-]CH_2OH
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)NH(Pr)
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)NHEt
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)NH(Bu)
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)(3-HO-Ph)
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)(4-HO-Ph)
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[2-(CH_2OH)-1-(c-penten)-1-yl]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[2-(CH_2OH)-1-(c-hexen)-1-yl]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[1-Nos-Pid-4-yl]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[Pid-4-yl]
H	H	4-Cl-Bn	R	2	1	c-Pen	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Hep	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	i-Pr	S	$C(O)CH(Me)_2$

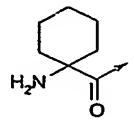
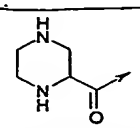
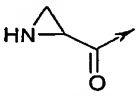
H	H	4-Cl-Bn	R	2	1	c-Hex-CH_2	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Pen	R	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	S	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Br-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	4-Br-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-MeO-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	4-MeO-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	3,4-diCl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	4-F-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	4-F-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Me-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-HO-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	(c-Hex)-CH_2	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	(indol-2-yl)- CH_2	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	i-Bu	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	$NH_2C(O)CH_2$-	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	2,3- diF-Ph	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	2,4- diF-Ph	S	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	2,3- diF-Ph	R	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	2,4- diF-Ph	R	$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)NH(CH_2)_4NH_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)NH(CH_2)_3NH_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)NH(CH_2)_2NH_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)NH(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)NH(CH_2)_2OMe$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[(3S)-3-(OH)-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[(2S)-2-($HOCH_2$)-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)C(Me)CH_2OH$
H	H	4-Cl-Bn	R	2	1	2,3-diF-Ph	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	3,5-diMe-Ph	R,S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	2,3-diF-ph	R,S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-Me-Ph	R,S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-t-Bu-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4,4-diF-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-F-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-*trans*-Et-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-*cis*-Et-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-oxo-c-Hex	S	$C(O)C(Me)_2CH_2OH$

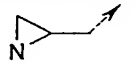
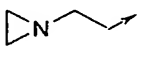
H	H	4-Cl-Bn	R	2	1	4-OH-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	Spiro[2.5]octane	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-Pid-1-yl	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	4-Ph-c-Hex	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	Ph	R,S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	2-adamantyl	S	$C(O)C(Me)_2CH_2OH$
H	H	4-F-Bn	R	2	1	c-Hex	S	C(O)[(R)-CH(Me)CH_2OH]
H	H	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	C(O)[C(Me)(CH_2-$OH)_2$]
H	H	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	C(O)[C(Me)(CH_2-$OH)_2$]
H	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	C(O)[C(Me)(CH_2-$OH)_2$]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[C(OH)(i-Pr)]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[$CH_2C(Me)_2$-OH]
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)(-$(CH_2)_2$-)C(O)OH
H	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)(-$(CH_2)_2$-)C(O)OMe
H	H	4-Cl-Bn	R	2	1	Pid-4-yl	S	$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	2-(CH_2OH)-1-(c-peten)1-yl
H	H	4-Cl-Bn	R	2	1	c-Hex	S	2-(CH_2OH)-1-(c-hexen)1-yl
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)N[(CH)_2OH]_2$
H	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)N[(CH)_3OH]_2$
Me	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
Me	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-t-Bu-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4,4-diF-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	Spiro[2.5]octane	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-F-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-*trans*-Et-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-*cis*-Et-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	C(O)[C(Me)(CH_2-$OH)_2$]
Me	H	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	C(O)[C(Me)(CH_2-$OH)_2$]
Me	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	C(O)[C(Me)(CH_2-$OH)_2$]
Me	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	C(-CH_2CH_2)CH_2OH
Me	H	Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$

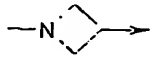
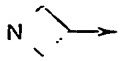
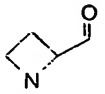
Me	H	4-F-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Me-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-MeO-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
i-Pr	H	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
i-Pr	H	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
i-Pr	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
i-Pen	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
Me	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_3$
Me	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	Me	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	Me	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	Me	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	Me	4-Cl-Bn	R	2	1	4-*trans*-Et-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	Me	4-Cl-Bn	R	2	1	4-*cis*-Et-c-Hex	S	$C(O)C(Me)_2CH_2OH$
Me	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)(CH_2OH)_2$
Me	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OMe)$
Me	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OMOM)$
i-Pr	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)[(R)\text{-}CH(Me)CH_2OH]$
Me	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)[(R)\text{-}CH(Me)CH_2OH]$
Me	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
Me	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)(\text{-}CH_2OC(O)OCH_2\text{-})$
Me	Me	4-Cl-Bn	R	2	1	4-*trans*-Me-c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
Me	Me	4-Cl-Bn	R	2	1	4-*cis*-Me-c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
Me	Me	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)[C(Me)(CH_2OH)_2]$
Me	Me	Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OH)$
Me	Me	4-F-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OH)$
Me	Me	4-Me-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OH)$
Me	Me	4-MeO-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OH)$
Me	Me	4-MeO-Bn	R	2	1	4-t-Bu-c-Hex	S	$C(O)C(Me)_2(CH_2OH)$
Et	Et	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$

i-Pr	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$-(CH_2)_5-$		4-MeO-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$MeO-(CH_2)_2-$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$HO(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Ac	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$MeSO_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
(iPr)C(O)	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
EtC(O)	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[(R)-CH(Me)CH_2OH]
Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$HO(CH_2)_3C(O)$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$(Me)_2N$-Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
i-Bu	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$-(CH_2)_4-$		4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$-(CH_2)_5-$		4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$NH_2-(CH_2)_4$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$HOCH_2C(Me)_2C(O)$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
imidazol-2-yl	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
imidazol-4-yl	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$HO(CH_2)_4$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
PrC(O)	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
Pyd-3-yl	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
(S)Pyd-2-CH_2-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$MeOC(O)CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
DTic	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$NH_2-(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$(Me)HN-(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
(S)Pyd-2-CH_2	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)[2-(CH_2OH)-1-(c-penten)-1-yl]
$(Me)_2NC(O)-CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$NH_2C(O)-CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
MeO_2C-CH_2	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
HO_2C-CH_2	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
N-Me-Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
N-diMe-Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
N-Ac-Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
N-Ms-Gly	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
(R)Ala	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
β-Ala	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
β-Ala	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_3$
N-Me-β-Ala	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
N-diMe-β-Ala	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$NH_2(CH_2)_4$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
(S)Ala	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
(S)His	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$

(S)His	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(Me)$_3$
N-Me-(S)His	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
N-Ac-(S)His	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
N-Ac-(S)His	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(Me)$_3$
N-Ms-(S)His	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)His	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(S)Phe	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Phe	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Pro	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Pro	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(Me)$_3$
N-Me-(R)Pro	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(Me)$_3$
(S)Pro	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Pid-2-CO	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Pid-2-CO	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)C(Me)$_3$
N-Me-(R)Pid-2-CO	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
N-Ac-(R)Pid-2-CO	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(S)Pid-2-CO	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Tic	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Tic	H	Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(S)Tic	H	4-Cl-Bn	R	2	1	c-Hex	R	C(O)CH(Me)$_2$
cis-Dic	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$

	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$HO\text{-}CH_2\text{-}C(O)$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$HO\text{-}C(O)CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$HO\text{-}C(O)CH_2$	$HO\text{-}C(O)CH_2$	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$MeOC(O)CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_3$
$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	2,3- diF-Ph	R	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	2,4- diF-Ph	R	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Pen	S	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	H	$(c\text{-}Hex)\text{-}CH_2\text{-}$	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)Pyd\text{-}2\text{-}CH_2$	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)\text{-}1\text{-}Me\text{-}Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)\text{-}1\text{-}Me\text{-}Pyd\text{-}2\text{-}CH_2$	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)\text{-}1\text{-}Ac\text{-}Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(S)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(S)\text{-}1\text{-}Me\text{-}Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)Pid\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)\text{-}1\text{-}Me\text{-}Pid\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(R)\text{-}1\text{-}Me\text{-}Pid\text{-}2\text{-}CH_2$	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(S)Pid\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(S)\text{-}1\text{-}Me\text{-}Pid\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$NH_2\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$NH_2\text{-}(CH_2)_2$	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)N\text{-}(CH_2)_2$	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)CH(Me)_2$
$(Me)N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	R	$C(O)C(Me)_3$
$(Me)_2N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)_2N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_3$
$(Me)_2N\text{-}(CH_2)_2$	H	Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)_2N\text{-}(CH_2)_2$	H	$(c\text{-}Hex)\text{-}CH_2\text{-}$	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)_2N\text{-}(CH_2)_2$	Me	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Me)N\text{-}(CH_2)_2\text{-}$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$(Me)_2N\text{-}(CH_2)_2\text{-}$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)CH_2OH$

$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OH$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)(CH_2OH)_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2[CH_2N(Me)_2]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OMe$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH_2OMOM)$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OBn$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2[CH_2O(i\text{-}Bu)]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OPh$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2$-SPh
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OCOPh$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2[CH_2OCO(c\text{-}Hex)]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OCOBn$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2CH_2OCOBu$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2[CH_2OCO(i\text{-}Pr)]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2[CH_2OCO(2,5diF\text{-}Ph)]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2OAc$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)[2\text{-}(HOCH_2)\text{-}1\text{-}(c\text{-}penten)\text{-}1\text{-}yl]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)[(3S)\text{-}3\text{-}(OH)\text{-}Pyd\text{-}1\text{-}yl]$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CHO)$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)C(Me)_2(CH{=}N\text{-}OMe)$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	2,3-diF-Ph	S	$C(O)C(Me)_2(CH_2OH)$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	2,3-diF-Ph	S	$C(O)N(Me)_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	4-*cis*-Mec-Hex	S	$C(O)C(Me)_2CH_2OH$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	1	4,4-diMe-c-Hex	S	$C(O)C(Me)_2CH_2OH$
$AcNH\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$(Et)_2N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
$[Me(Et)]N\text{-}(CH_2)_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	$C(O)CH(Me)_2$

	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(R)Pyd-3-yl	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
Pid-4-yl	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
Pid-4-yl	Me	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
1-Me-Pid-4-yl	Me	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
(Me)$_2$N-CH=	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
Pyd-1-(CH$_2$)$_2$	H	4-Cl-Bn	R	2	1	c-Hex	S	C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)C(Me)$_3$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)OMe
H	H	4-Cl-Bn	R	2	2	c-Hex		CH$_2$C(O)OMe
H	H	4-Cl-Bn	R	2	2	c-Hex		CH$_2$C(O)N(Me)$_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)$_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		Gly
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)$_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)NH(i-Pr)
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)(i-Pr)
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)NH(Bu)
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)(Bu)
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)NH(c-Hex)
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)NHPh
H	H	4-Cl-Bn	R	2	2	c-Hex		C(S)NH(Et)
H	H	4-Cl-Bn	R	2	2	c-Hex		C(S)N(Me)(Et)
H	H	4-Cl-Bn	R	2	2	c-Hex		SO$_2$Me
H	H	4-Cl-Bn	R	2	2	c-Pen		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	c-Hep		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2-MeO-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	3-MeO-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2-Cl-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2-F-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	3-F-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	4-F-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2,4- diF-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2,5- diF-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2,6- diF-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	3,4- diF-Ph		C(O)CH(Me)$_2$
H	H	4-Cl-Bn	R	2	2	2-F-4-MeO-Ph		C(O)CH(Me)$_2$

H	H	4-Cl-Bn	S	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	4-Br-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	3,4-diCl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	4-F-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
H	H	4-HO-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	4-MeO-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
H	H	(c-Hex)-CH_2	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	3,4-diCl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	4-F-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
H	H	4-HO-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	4-MeO-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
H	H	(c-Hex)-CH_2	R	2	2	c-Hex		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	2	2	2,3-diF-Ph		$C(O)N(Me)(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	2,3-diF-Ph		$C(O)N(Me)(CH_2)_2OMe$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)CH_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[2-(CH_2OH)-1-(c-penten)-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[2-(CH_2OH)-1-(c-hexen)-1-yl]
H	H	4-Cl-Bn	R	2	2	2,3-diF-Ph		$C(O)C(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(n\text{-}Pr)(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(c\text{-}Pr)(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(i\text{-}Pr)(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)(CH_2)_2OMe$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)NH(CH_2)_2OMe$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2OMe$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe]_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OH]_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)OMe
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)[C(Me)_2CH_2NH_2]$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](\cdot CH_2)_2F$
H	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)(CH_2)_2F$

H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_3OH]_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OMe](CH_2)_3OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F](CH_2)_3OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F](CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F]_2$
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$OMe
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$OH
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$F
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$F
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(n-Pr)$(CH_2)_2$OH
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(c-Pr)$(CH_2)_2$OH
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OMe](CH_2)_2$OH
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$OMe
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OMe](CH_2)_2$F
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$F
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F](CH_2)_3OH$
H	H	4-F-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F]_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3S)-3-(OH)-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3R)-3-(OH)-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(2R)-2-$(HOCH_2)$-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(2S)-2-$(HOCH_2)$-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3R)-3-amino-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3S)-3-amino-Pyd-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3R)-3-(OH)-Pid-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3S)-3-(OH)-Pid-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[4-(OH)-Pid-1-yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[4-amino-Pid-1-

								yl]
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)(-$(CH_2)_2$-)C(O)OH
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)(-$(CH_2)_2$-)C(O)OMe
H	H	4-Cl-Bn	R	2	2	4-*cis*-Me-c-Hex		C(O)C$(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	2	4-*trans*-Me-c-Hex		C(O)C$(Me)_2CH_2OH$
H	H	4-Cl-Bn	R	2	2	4-diMe-c-Hex		C(O)(-$(CH_2)_2$-)C(O)OMe
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2F$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3F$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2OH$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$(Et)_2$
H	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)[C(O)$(Me)_2CH_2OH$]
Me	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH$(Me)_2$
Me	H	4-Cl-Bn	R	2	2	c-Hex		C(O)C$(Me)_3$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N$(Et)_2$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2OH$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(c-Pr)$(CH_2)_2OH$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2OH$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2OMe$]($CH_2)_2OH$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2OH]_2$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2F$]($CH_2)_2OH$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2O$Me
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2F$]($CH_2)_2OMe$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2F$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3F$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3OH$
Me	Me	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2OMe$]($CH_2)_3OH$
Me	Me	4-F-Bn	R	2	2	c-Hex		C(O)N$(Et)_2$
Me	Me	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2OH$
Me	Me	4-F-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2OH$
Me	Me	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2OH]_2$
Me	Me	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2F$]($CH_2)_2OMe$
Me	Me	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3OH$
MeO_2C-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH$(Me)_2$
HO_2C-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH$(Me)_2$

N-diMe-Gly	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Ala	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
β-Ala	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
N-diMe-β-Ala	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(S)His	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Pro	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
N-Me-(R)Pro	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Tic	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
MeO_2C-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
HO_2C-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
N-diMe-Gly	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Ala	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
β-Ala	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
N-diMe-β-Ala	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(S)His	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Pro	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
N-Me-(R)Pro	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Tic	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)C(Me)_3$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,4- diF-Ph		$C(O)CH(Me)_2$
(S)Pyd-2-CH_2	H	4-F-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
(2R,4S)-4F-Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		$C(O)CH(Me)_2$
(R)Pyd-2-CH_2-	H	4-Cl-Bn	R	2	2	2,3-diF-Ph		$C(O)C(Me)_2CH_2OH$
(R)Pyd-2-CH_2-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)C(Me)_2CH_2OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(i\text{-}Pr)(CH_2)_2OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](CH_2)_2OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2F](CH_2)_2OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2F$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_3OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(n\text{-}Pr)(CH_2)_2OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OH]_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)OMe
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)[C(Me)_2CH_2NH_2]$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2OH$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe]_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(c\text{-}Pr)(CH_2)_2OH$

(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3S)-3-(OH)-Pyd-1-yl]
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(2R)-2-($HOCH_2$)-Pyd-1-yl]
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[4-(OH)-Pid-1-yl]
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(3R)-3-(OH)-Pid-1-yl]
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$_2$
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2$OH
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OH]$_2$
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$F]$(CH_2)_2$OMe
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$F
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OMe]$(CH_2)_2$OH
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)[(3S)-3-(OH)-Pyd-1-yl]
(R)Pyd-2-CH_2	H	4-F-Bn	R	2	2	c-Hex		C(O)[(2R)-2-($HOCH_2$)-Pyd-1-yl]
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		N(Me)[$C(Me)_2CH_2OH$]
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$_2$
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(c-Pr)$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OMe]$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OH]$_2$
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$F]$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$OMe
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$F]$(CH_2)_2$OMe
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$F
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OMe]$(CH_2)_3$OH
1-Pyd-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$_2$
1-Pyd-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2$OH
1-Pyd-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OH]$_2$
1-Pyd-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$F]$(CH_2)_2$OMe
1-Pyd-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH

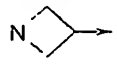
1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$F
(R)-3-BnO-1-pyd-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$F
(S)-3-BnO-1-pyd-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
(i-Pr)(Me)N-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$F
NH_2-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OH]_2$
(Me)NH-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OH]_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)C(Me)$_3$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		C(O)CH(Me)$_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,4- diF-Ph		C(O)CH(Me)$_2$
(S)Pyd-2-CH_2	H	4-F-Bn	R	2	2	2,3- diF-Ph		C(O)CH(Me)$_2$
(2R,4S)-4F-Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		C(O)CH(Me)$_2$
(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3- diF-Ph		C(O)CH(Me)$_2$
(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,4- diF-Ph		C(O)CH(Me)$_2$
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3-diF-Ph		C(O)N(Me)$(CH_2)_2$OH
(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2	2	2,3-diF-Ph		C(O)N(Me)$(CH_2)_2$OMe
(R)-1-Me-Pid-2-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(S)-1-Me-Pid-3-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(R)-1-Me-Pid-3-CH_2	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(R)Pyd-3-yl	H	4-Cl-Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(R)Pyd-3-yl	H	Bn	R	2	2	c-Hex		C(O)CH(Me)$_2$
(S)Pyd-3-yl	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$_2$
(S)Pyd-3-yl	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$OH
(S)Pyd-3-yl	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
2-oxo-1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
2-oxo-1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
3-OH-1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$F
3-OH-1-Pyd-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$_2$
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(c-Pr)$(CH_2)_2$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OMe](CH_2)_2OH$
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2OH]_2$
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F](CH_2)_2OH$
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)$(CH_2)_2$OMe
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N$[(CH_2)_2F](CH_2$

								$)_2$OMe
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$F
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OMe]($CH_2)_3$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N$(Et)_2$
(i-Pr)HN-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_2$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N(i-Pr)$(CH_2)_2$OH
(i-Pr)HN-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$OH]$_2$
(i-Pr)HN-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		C(O)N[$(CH_2)_2$F](CH_2)$_2$OMe
(i-Pr)HN-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Et)$(CH_2)_3$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N$(Et)_2$
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(Et)$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(c-Pr)$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(i-Pr)$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N[$(CH_2)_2$OMe]$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N[$(CH_2)_2$OH]$_2$
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N[$(CH_2)_2$F]$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(Me)$(CH_2)_2$OMe
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N[$(CH_2)_2$F]$(CH_2)_2$OMe
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(Et)$(CH_2)_3$F
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(Et)$(CH_2)_2$F
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N(Et)$(CH_2)_3$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		N[$(CH_2)_2$OMe]$(CH_2)_3$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		N$(Et)_2$
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		N(Et)$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		N(i-Pr)$(CH_2)_2$OH
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		N[$(CH_2)_2$OH]$_2$
(S)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		N[$(CH_2)_2$F]$(CH_2)_2$OMe
(S)-3-OH-Pyd-1-	H	4-F-Bn	R	2	2	c-Hex		N(Et)$(CH_2)_3$OH

$(CH_2)_2$								
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)_2$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(c\text{-}Pr)(CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(i\text{-}Pr)(CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2OMe](CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2OH]_2$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2F](CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(Me)(CH_2)_2OMe$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2F](CH_2)_2OMe$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_3F$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2F$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_3OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2OMe](CH_2)_3OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		$N(Et)_2$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		$N(i\text{-}Pr)(CH_2)_2OH$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		$N[(CH_2)_2OH]_2$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		$N[(CH_2)_2F](CH_2)_2OMe$
(R)-3-OH-Pyd-1-$(CH_2)_2$	H	4-F-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_3OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)_2$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(c\text{-}Pr)(CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(i\text{-}Pr)(CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2OMe](CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2OH]_2$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2F](CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Me)(CH_2)_2OMe$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2F](CH_2)_2OMe$

2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_3F$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2F$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_3OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$N[(CH_2)_2OMe](CH_2)_3OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$N(Et)_2$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$N(i\text{-}Pr)(CH_2)_2OH$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$N[(CH_2)_2OH]_2$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$N[(CH_2)_2F](CH_2)_2OMe$
2-oxo-1-pyd--$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$N(Et)(CH_2)_3OH$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(c\text{-}Pr)(CH_2)_2OH$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2OH$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe]_2$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OH]_2$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2F](CH_2)_2OH$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)(CH_2)_2OMe$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2F](CH_2)_2OMe$
Mor-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2F$
Mor-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2OH$
Mor-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(i\text{-}Pr)(CH_2)_2OH$
Mor-$(CH_2)_2$-	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OH]_2$
NH_2-$(CH_2)_2$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)CH(Me)_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)N(Me)OMe
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2$-OH
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(n\text{-}Pr)(CH_2)_2$-OH
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2$-$OH]_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2$-$OMe]_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)[(2R)-2-$(HOCH_2)$-Pyd-1-yl]
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		C(O)(4-amino-Pid-1-yl)
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)(CH_2)_2$-OH
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Me)(CH_2)_2$-OMe
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)_2$
$(Me)_2N$-$(CH_2)_2$-	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(i\text{-}Pr)(CH_2)_2OH$

$(Me)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](CH_2)_2OH$
$(Me)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2F](CH_2)_2OH$
$(Me)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2F$
$(Me)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_3OH$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		C(O)N(Me)OMe
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2$-OH
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(n-Pr)(CH_2)_2$-OH
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2-OH]_2$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2-OMe]_2$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(i-Pr)(CH_2)_2OH$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](CH_2)_2OH$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2F](CH_2)_2OH$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2F$
$(Me)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_3OH$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_3OH$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2$-OH
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(n-Pr)(CH_2)_2$-OH
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2-OH]_2$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2-OMe]_2$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(i-Pr)(CH_2)_2OH$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](CH_2)_2OH$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2F](CH_2)_2OH$
$(Et)_2N-(CH_2)_2-$	H	4-Cl-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2F$
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_3OH$
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(Et)(CH_2)_2$-OH
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(n-Pr)(CH_2)_2$-OH
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2-OH]_2$
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2-OMe]_2$
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N(i-Pr)(CH_2)_2OH$
$(Et)_2N-(CH_2)_2-$	H	4-F-Bn	R	2	2	c-Hex		$C(O)N[(CH_2)_2OMe](CH_2)_2OH$
H	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)C(Me)_3$
H	H	4-Cl-Bn	R	1	1	c-Hex		C(O)OMe

H	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)N(Me)_2$
H	H	4-Cl-Bn	R	1	1	c-Hex		$S(O)_2Me$
H	H	4-Cl-Bn	R	1	1	c-Pen		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	1	1	c-Hep		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	1	1	i-Pr		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	1	1	(c-Hex)Me		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	1	1	2-Me-(c-Hex)		$C(O)CH(Me)_2$
H	H	4-Cl-Bn	R	1	1	i-Bu		$C(O)CH(Me)_2$
MeO_2C-CH_2	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
HO_2C-CH_2	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
Gly	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
N-diMe-Gly	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
(S)His	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
N-BOC-(S)His	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
(R)Pro	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
N-Me-(R)Pro	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
(S)Pro	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
(R)Pid-2-CO	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
N-Me-(R)Pid-2-CO	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
(R)Tic	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
$(R)Pyd-2-CH_2$	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
$Pyd-1-(CH_2)_2$	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
$(R)-1-Me-Pid-2-CH_2$	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
$(Me)_2N-(CH_2)_2$	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
$(R)-Pid-2-CH_2$	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$
$(Me)_2N-(CH_2)_2$	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)C(Me)_3$
	H	4-Cl-Bn	R	1	1	c-Hex		$C(O)CH(Me)_2$

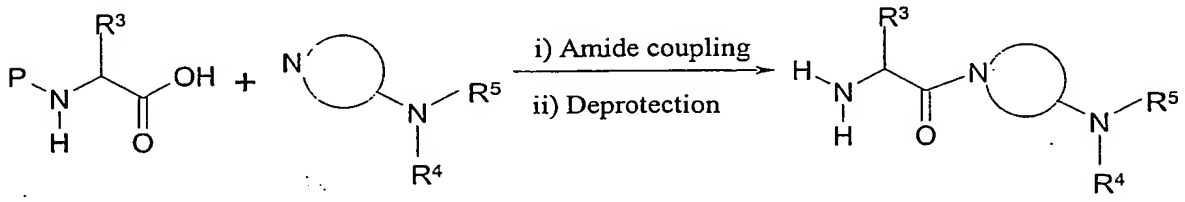
The compounds according to the present invention also can form pharmaceutically acceptable salts. These pharmaceutically acceptable salts include acid forming non-toxic acid addition salt containing pharmaceutically acceptable anion, for example, inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid, hydroiodic acid, and the like; organic carboxylic acid such as tartaric, formic, citric, acetic, trichloroacetic, trifluoroacetic, gluconic, benzoic, lactic, fumaric, maleic, and the like; acid-addition salts formed by sulfonic acid such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or naphthalenesulfonic acid, and the like; preferably, acid-addition salts formed by sulfuric acid, methansulfonic acid or hydrohalic acid, and the like. The compounds of formula 1 according to the present invention can be converted to its salts by customary method.

Also, the compounds according to the present invention can have asymmetric carbon center, and so can be present as R or S isomeric forms, racemates, diastereomeric mixtures, and individual diasteromers. The present invention encompasses all these isomeric forms and mixtures.

The compounds according to the present invention can be prepared according to the procedures explained in the following Schemes 1 - 9. In the following Schemes, compounds of general formula (3), (6), (11), (12), (13), (14), (17), (18), (22), (24), (40) and (43) represent representative compounds of formula 1.

Compounds of formula (3) can be prepared by coupling protected amino acids (1) (P represents protecting groups, such as BOC, Cbz, Fmoc, etc.) with substituted amino-cyclic amine derivatives (2) (cyclic amine represent pyrrolidine, piperidine, or azetidine) under standard peptide coupling conditions, as illustrated in Scheme 1. The protected amino acids (1), starting materials, are either commercially available or may be prepared by known methods (Williams, R. M., Synthesis of Optically Active a-Amino Acids, Pergamon Press: Oxford, 1989). Similarly, the amino-cyclic amine derivatives (2) can be prepared following literature methods described for analogous compounds.

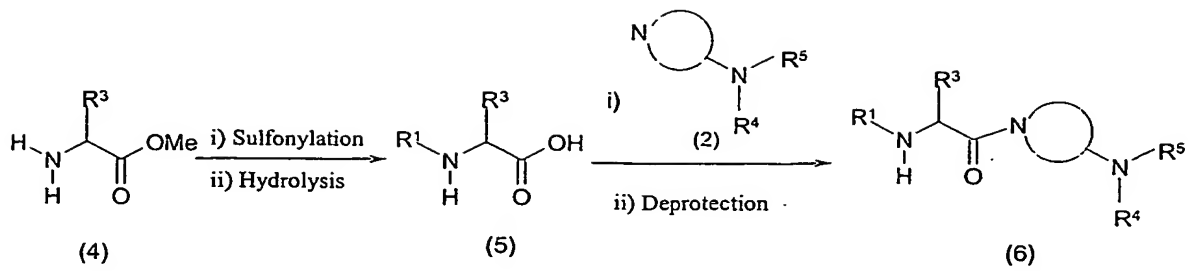
Scheme 1



(1) (2) (3)

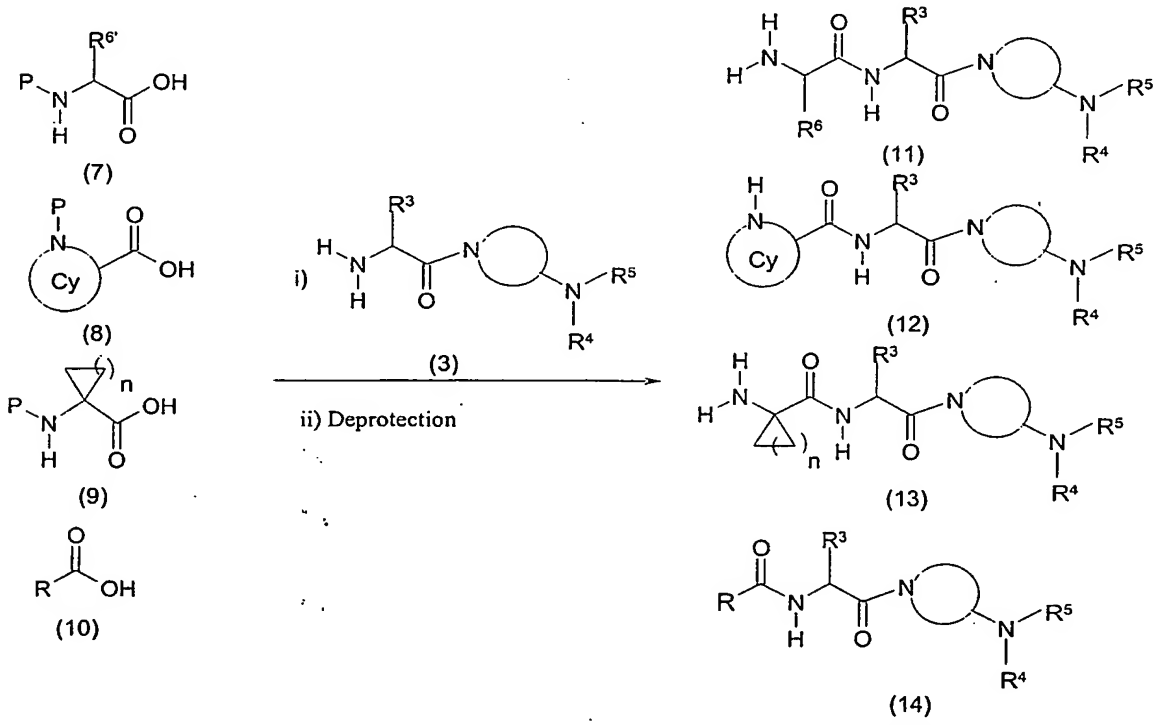
Compounds of formula (6) may be prepared by coupling N-substituted amino acid derivatives (5) with amino-cyclic amine derivatives (2), as illustrated in Scheme 2. Alkyl, acyl, or sulfonyl substituted amino acid derivatives (5) can be converted to amino acid derivatives (6) by hydrolysis in the presence of base.

Scheme 2



Compounds of formula (10), (11), (12), and (14) may be prepared by coupling protected amino acid derivatives (7), (8), (9), and (10) with the compounds of formula (3) as shown in Scheme 3 [Cy in compound (8) represents pyrrolidine, azetidine, aziridine, piperidine, etc.]. Protected amino acid derivatives (7), (8) and (9) are either commercially available or can be prepared by general protection reaction from various amino acids.

Scheme 3

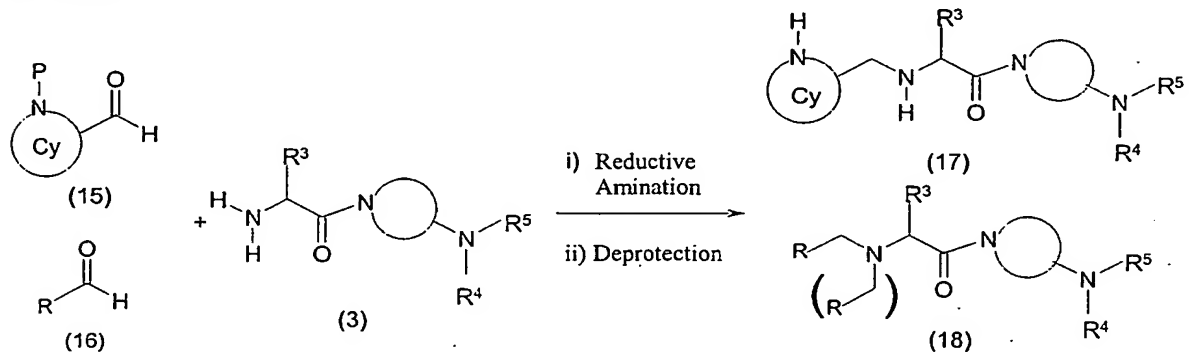


In the above Reaction Scheme 3, $R^{6'}$ is same as defined above in R^6, and R represents alkyl or protected aminoalkyl.

Alkylated amine compounds of formula (17) or (18) can be prepared through reductive amination of protected amino aldehydes of formula (15) with compounds of

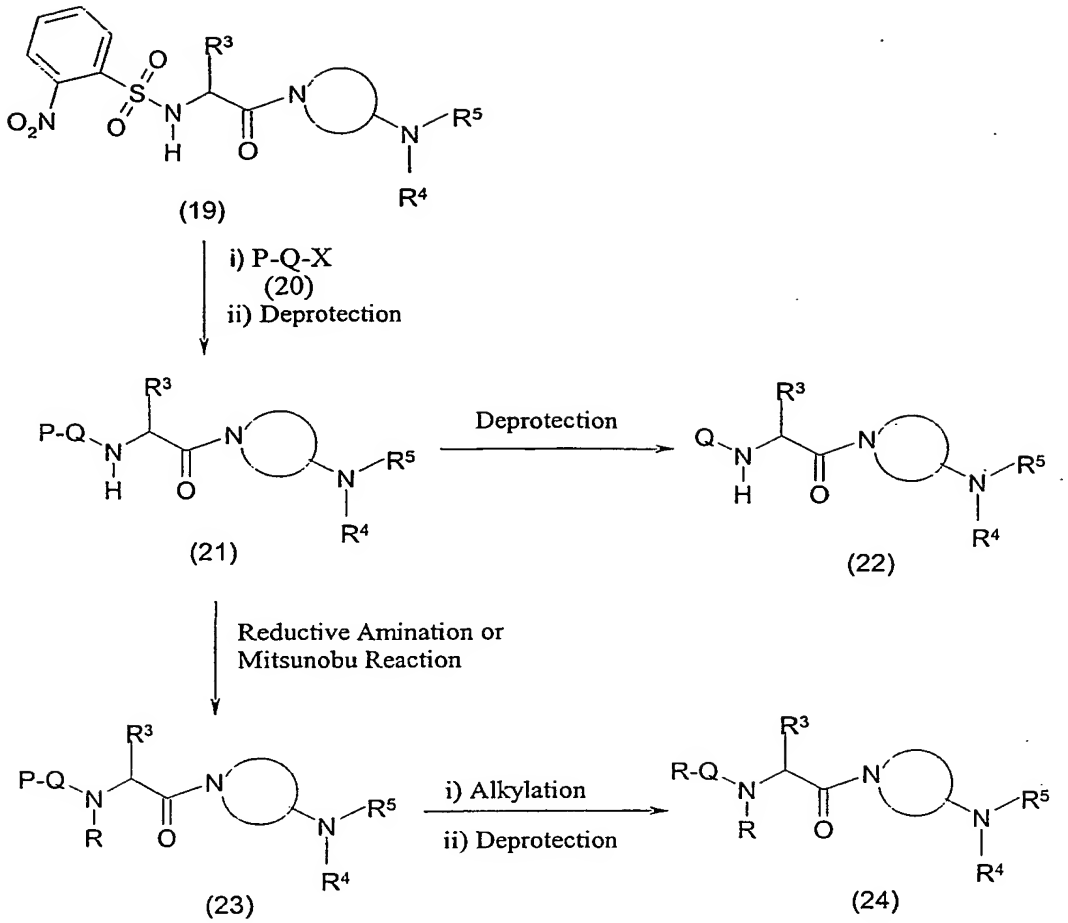
formula (3) prepared in Scheme 1, as shown in Scheme 4. As a reducing agent in the reductive amination, $NaHB(OAc)_3$ or $NaBH_3CN$ may be used, and DCE, DMF, methanol, DCM, etc. may be used as a solvent, but the reaction reagents and solvents are not limited to these. The protected amino aldehydes (15) is either commercially available or can be prepared by known methods such as reduction of thioesters or oxidation of amino alcohols. Compounds of formula (16) are general alkyl aldehydes, amino aldehydes or hydroxy aldehydes whose amino or alcohol group is either substituted or protected. These compounds are either commercially available or can be prepared by protection reaction. Mono- or di- substituted compounds (18) can be prepared by reductive amination and deprotection.

Scheme 4



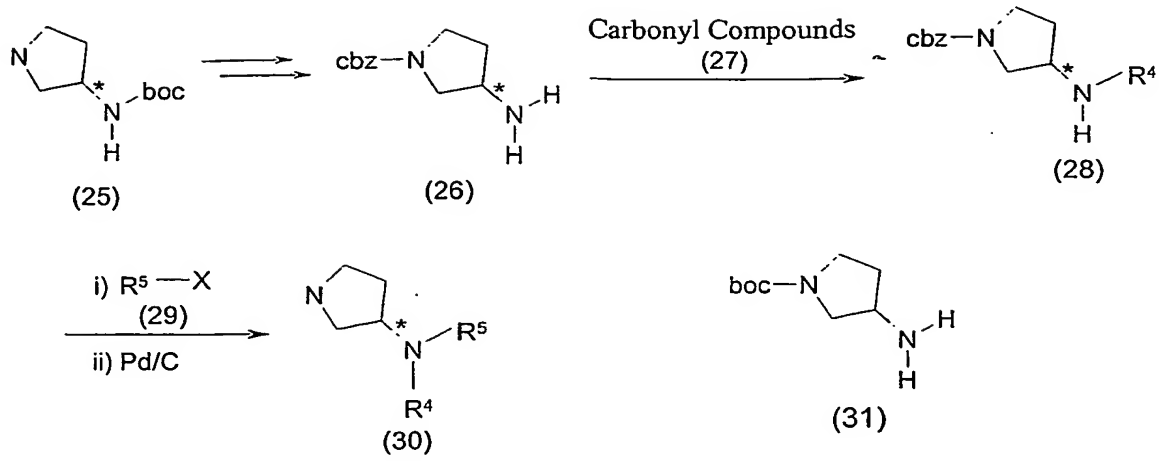
Compounds of formula (22), (23) and (24) can be prepared as shown in the following Scheme 5. Nitrobenzenesulfonyl protected intermediates of formula (19) can be converted to the compounds of formula (21) by alkylation or reductive amination (*Tetrahedron Lett.*, **1995**, *36*, 6373-6374). In compounds of formula (20) such as dimethylaminoethylchloride or N-BOC-2-aminoethyl-chloride, Q represents aminoalkyl or alkylated aminoalkyl, and X represents halogen. Compounds of formula (23) can be prepared through reductive amination of compounds of formula (21) and then converted into the compounds of formula (24) by alkylation.

Scheme 5



3-Disubstituted amino pyrrolidine derivatives (30) can be prepared as illustrated in Scheme 6. Compound (26) prepared from the commercially available compound (25) can be converted to compounds of formula (28) by reductive amination. Compounds of formula (30) can be prepared by acylation, amide coupling, or alkylation of compounds formula (28), and removing cbz group. Compounds of formula (30) can also be prepared from compound (31) using the similar method illustrated in Scheme 7.

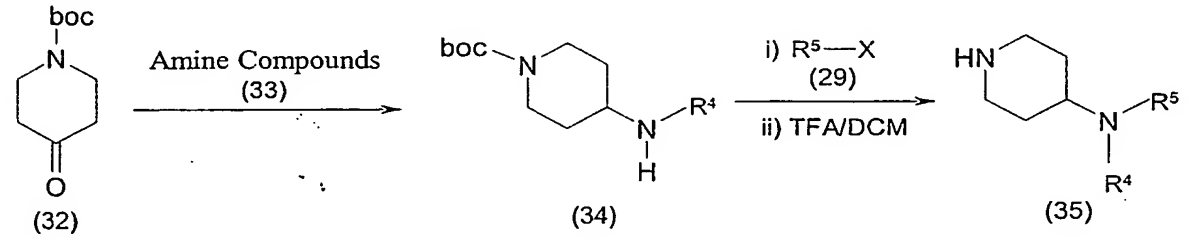
Scheme 6



In the above reaction scheme, compound (29) represents alkylhalide, substituted alkylhalide, carboxylic acid, or acid chloride; and R^6 is the same as defined above; and X represents OH, Br, Cl, etc.

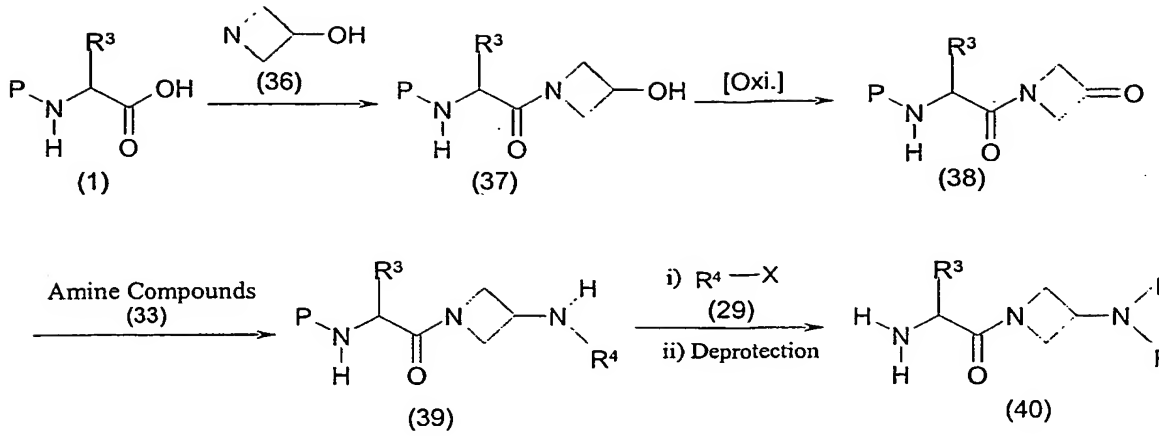
4-Disubstituted piperidine derivatives (35) can be prepared as illustrated in Scheme 7. Compounds of formula (34) can be prepared by introducing various amine groups into compound (32) by reductive amination. Amino piperidine derivatives (35) can be prepared by acylation, amide coupling reaction, or akylation of compounds of formula (34), and deprotection.

Scheme 7



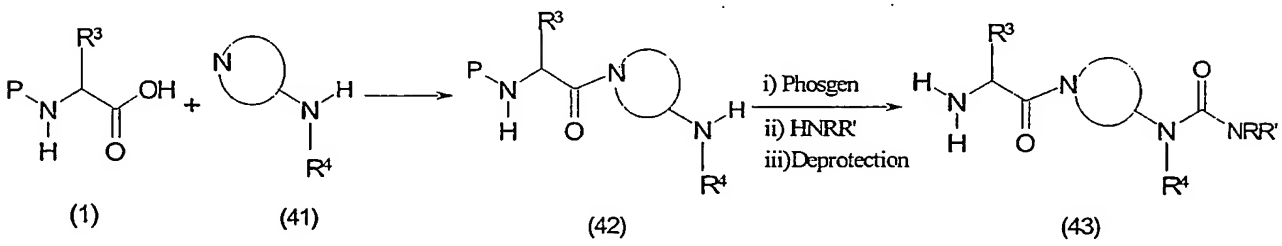
Azetidine derivatives can be prepared by the method illustrated in Scheme 8. Coupling of protected amino acid derivatives (1) with 3-azetidinol gives compounds of formula (37) which can then be converted into carbonyl compounds of formula (38). Compounds of formula (40) can be prepared from compounds of formula (38) via reductive amination, acylation, amide coupling, and alkylation.

Scheme 8



Urea derivatives can be prepared by the method illustrated in Scheme 9. Coupling of protected amino acid derivatives (1) with cyclic amine derivatives (41) produces compounds of formula (42). Compounds of formula (42) can be converted to urea derivatives (43) by phosgene-mediated amide coupling.

Scheme 9



In the above reaction scheme, NRR' represents substituted or unsubstituted amino group among the definition of R^7, R^8, or R^9.

It is preferable to carry out each step of the above methods in conventional solvents which do not have significant deleterious effect to the reaction, and particularly preferable to use one or more kinds selected from the group consisting of, but not limited to, dimethylformamide, dimethylacetamide, tetrahydrofuran, methylene chloride, and chloroform.

Deprotection reaction can be carried out in the presence of strong acid such as hydrochloric acid, trifluoroacetic acid, etc., in the presence of amine base such as triethylamine, diisopropylethylamine, etc., or by hydrogenation. Specific reaction conditions are described in T. W. Green & G. M. Wuts Protective Groups in Organic Synthesis, Chapter 7, pp 309-405.

Known coupling agents usable in coupling reaction are, but are not limited to, carbodiimides such as dicyclohexylcarbodiimide (DCC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), 1,1'-dicarbonyldiimidazole (CDI), etc. which are used in a mixture with 1-hydroxybenzotriazole (HOBT) or 1-hydroxy-7-azabenzotriazole (HOAT); bis-(2-oxo-3-oxazolidinyl)-phosphinic acid chloride (BOP-Cl), diphenylphosphorylazide (DPPA), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU), etc.

General separation of mixtures is conducted by column chromatography, and in case of final compound, separation can be done by recrystallization or normal or reverse HPLC (Waters, Delta Pack, 300x50 mm I.D., C18 5 ㎛, 100A). When recrystallization or HPLC is used for purification, the compound can be obtained in the form of trifluoroacetic acid salt. Hydrochloric acid salt can be obtained by using ion exchange resin.

After the above reactions according to the present invention are completed, products can be separated and purified by customary work-up methods, for example, chromatography, recrystallization, etc.

The compounds of the present invention have potent agonistic effect against melanocortin receptors, and so the present invention provides a melanocortin receptor agonistic composition comprising the compound of formula 1 as active ingredients together with pharmaceutically acceptable carrier. In particular, the composition according to the present invention has potent effect for the prevention and treatment of, but not limited to, diabetes, erectile dysfunction, obesity, and inflammation.

When the compounds according to the present invention are administered for clinical purpose, a preferable daily dose would be within the range of 0.01 ~ 10 mg/ kg body weight as unitary dosage or separated dosage. However, a dosage level specific

to individual patients can be varied, depending upon specific compound to be used, weight, sex, health condition, diet, administration time and method of drug, excretion rate, drug mixing, and severity of disease condition.

Any route depending on purpose can administer the compounds according to the present invention. Injection, and oral and nasal administration are preferred, but administration may be made through dermal, intraperitoneal, retroperitoneal, and rectal route.

Injectable preparation, for example, aqueous or oily suspension for sterile injection, can be prepared according to known method by using proper dispersants, wetting agents, or suspending agents. Solvents usable for this purpose are water, ringer's solution, and isotonic NaCl solution, and sterilized fixed oil is conventionally used as solvent or suspending media, too. Any non-irritable fixed oil including mono-, di-glyceride can be used for this purpose, and aliphatic acid such as oleic acid can be used for injectable preparation.

Solid dosage forms for oral administrations are capsules, tablets, pills, powders and granules, and in particular, capsules and tablets are useful. Capsules and tablets are preferable to be prepared as enteric coating. Solid dosage forms can be prepared by mixing compound (1) according to the present invention with one or more inert diluents such as sucrose, lactose, starch, etc., and carriers, for example, lubricants like magnesium stearate, disintegrants, binding agents, etc.

Abbreviations used in the above Description, and the following Preparations and Examples are as follows:

Ac	acetyl
Bn	benzyl
Bu	butyl
CBZ(Cbz)	benzyloxycarbonyl
BOC(Boc)	tert-butoxycarbonyl
Fmoc	9-fluorenylmethoxycarbonyl
c-Hep	cycloheptyl
c-Hex	cyclohexyl
c-Pr:	cyclopropyl

c-Pen	cyclopentyl
DAST	Diethylaminosulfur trifluoride
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethylazodicarboxylate
Dic	decahydroisoquioline-3-carboxylic acid
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	Dimethylsulfoxide
DTic	(D)-1,2,3,4-tetrahydriosoquinoline-3-carboxylic
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide HCl
Gly	Glycine
Hex	hexane
HOBt	1-hydroxybenzotriazole
HBTU	O-Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate
i-Bu	isobutyl
i-Pr	isopropyl
Mor	Morpholine
MOM	Methoxymethyl
Nos	2-Nitrobenzene sulfonyl
Ph	phenyl
Phe	phenylalanine
Pid	piperidine
Pro	proline
Pyd	pyrrolidine
TEA	triethylamine
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
Tic	1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

The following Intermediates further illustrate preparation of intermediates needed for synthesis of the compounds according to the present invention.

Interediate 1: (3S)-1-Cbz-3-aminopyrrolidine.

Step A: (3S)-1-Cbz-3-(N-BOC-amino)pyrrolidine

To a solution of (3S)-1-Cbz-3-(N-BOC-amino)pyrrolidine (5.00 g, 26.9 mmol) and TEA (7.54 mL, 53.8 mmol) in DCM (6 mL) was added CbzCl (5.50 g, 29.6 mmol) at rt. After 4 h, a saturated aqueous NH_4Cl solution was added and the reaction mixture was extracted with DCM followed by EtOAc. The organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/Hex = 1/2) to give the title compound (9.06 g, 96.1%).

MS [M+H] = 321 (M+1)

Step B: (3S)-1-Cbz-3-amino-pyrrolidine.

The product of Step A, (3S)-1-Cbz-3-(N-BOC-amino)pyrrolidine, (5.26 g, 16.4 mmol) was dissolved in EtOAc (50 mL) and treated with a saturated HCl in EtOAc (15 mL). After the reaction mixture was stirred at rt for 30min., the volatiles were removed to provide the title compound (4.11g, 98.1%) as a colorless solid. The crude product was used without further purification.

MS [M+1] = 221 (M+1)

Intermediate 2: (3S)-1-Cbz-3-(cyclohexylamino)pyrrolidine.

To a solution of (3S)-1-Cbz-3-aminopyrrolidine (4.11 g, 16.0 mmol) and cyclohexanone (2.36 g, 24.0 mmol) in DCE (50 mL) was slowly added $NaBH(OAc)_3$ (6.78 g, 32.0 mmol) at rt. The reaction mixture was quenched after 4h using a saturated aqueous $NaHCO_3$ solution and extracted with DCM followed by EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography (EtOAc/Hex = 2/1) to give the title compound (4.79 g, 98.1%).

MS [M+1] = 303 (M+1)

Intermediate 3: 4,4-Dimethyl-cyclohexan-1-one.

4,4-Dimethyl-cyclohexene-1-one (5 g, 52 mmol) and n-pentane (50 mL) were placed in a hydrogen reaction vessel and Pd/C (300 mg) was added. The hydrogen reaction vessel was purged three times with hydrogen and subsequently pressurized with hydrogen (25 psi). After shaking in a Parr hydrogenator for 30 min., the reaction mixture was filtered though Celite and the filtrate concentrated *in vacuo* to give the title compound.

MS[M+H] = 127 (M+1)

Intermediate 4: 1-BOC-4-piperidone.

To a solution of 4-piperidone (10 g, 100 mmol) and TEA (28.0 mL, 20 mmol) in DCM (2.00 ℓ) was added di-t-butyldicarbonate (30 g, 150 mmol) at rt. After 4 h,, the reaction mixture was concentrated *in vacuo* and the residue was diluted with 1N HCl (500 mL). The reaction mixture was extracted with EtOAc, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chomatography (EtOAc/Hex = 1/15) to give the title compound (19.1 g, 96.5%).

MS[M+H] = 200 (M+1)

Intermediate 5: Spiro[2,5]octanone.

Step A: 4,4-Methylene-1,1-ethyleneketal-4-spiro[2,5]octane

To a solution of DMSO (80 mL), filled with nitrogen, was added NaH (2.3 g, 58 mmol), and the reaction mixture was heated at 50 –60 °C. When the reaction solution turned light green, MeP $(Ph)_3Br$ (21.2 g, 60 mmol) was added, and the reaction solution was cooled to rt and stirred for 1 h. Cyclohexanedione monoethyleneketal (5.64 g, 36 mmol) was slowly added, and then the reaction mixture was heated to 40 °C and stirred for additional 2 h. The reaction solution was cooled to rt and a solution of diethyl ether/ice-water was added. The organic solution extracted with Et_2O was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chomatography (EtOAc/Hex = 1/5) to give the title compound (4.51 g, 82%).

MS[M+H] = 155 (M+1)

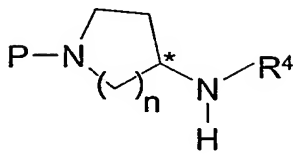
Step B: spiro[2,5]octanone

To a solution of 4,4-methylene-1,1-ethyleneketal-4-spiro[2,5]octane (4.5 g, 30 mmol), prepared by Step A, in Et_2O was added CH_2I_2 (12.0 mL, 150 mmol) and Zn-Cu (12.3 g, 48 mmol). The mixture was stirred at rt for 12 h, filtered, and diluted with 1N HCl solution. The organic material was extracted with diethyl ether, dried over $MgSO_4$ and then concentrated *in vacuo* to give the title compound. The crude product was used without further purification.

Intermediates 6~35.

The compounds below were prepared following the procedure described in Intermediate 2 using commercially available amines, carbonyl compounds, amine compound prepared in Intermediate 1, and carbonyl compounds prepared in

Intermediates 3, 4, and 5.



Intermediate	P	n	R^4	*	MS(M+1)
6	BOC	1	c-Hex	S	303
7	Cbz	1	c-Hex	R	303
8	Cbz	1	c-Pen	S	289
9	Cbz	1	c-Hep	S	317
10	Cbz	1	i-Pr	S	263
11	Cbz	1	(c-Hex)-CH_2-	S	317
12	Cbz	1	Ph	R,S	297
13	Cbz	1	4-Me-Ph	R,S	311
14	Cbz	1	3,5-diMe-Ph	R,S	325
15	Cbz	1	2-Adamantyl	S	355
16	Cbz	1	4-cis-Me-(c-Hex)	S	317
17	Cbz	1	4-trans-Me-(c-Hex)	S	317
18	Cbz	1	4,4-di-Me-(c-Hex)	S	331
19	Cbz	1	4-t-Bu-(c-Hex)	S	359
20	Cbz	1	4-*cis*-Et-(c-Hex)	S	331
21	Cbz	1	4-*trans*-Et-(c-Hex)	S	331
22	Cbz	1	N-BOC-Pip-4-yl	S	404
23	Cbz	1	4,4-ethyleneketal-(c-Hex)	S	361
24	Cbz	1	Spiro[2,5]octan-1-yl	S	329
25	Cbz	1	4-Ph-c-Hex	S	379
26	BOC	2	c-Hex		283
27	BOC	2	c-Pen		269
28	BOC	2	c-Hep		297
29	BOC	2	i-Pr		243
30	BOC	2	(c-Hex)-CH_2-		297
31	BOC	2	i-Bu		257

32	BOC	2	2-Me-c-Hex		297
33	BOC	2	4,4-diMe-c-Hex		311
34	BOC	2	4-*trans*-Me-c-Hex		297
35	BOC	2	4-*cis*-Me-c-Hex		297

Intermediate 36: (3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine.

Step A: (3S)-1-Cbz-3-[cyclohexyl (isobutyryl)amino]pyrrolidine

To a solution of (3S)-1-Cbz-3-(cyclohexylamino)pyrolidine (4.75 g, 15.1 mmol) and TEA (4.26 mL, 30.2 mmol) in DCM (50 mL) was added dropwise isobutyryl chloride (1.16 mL, 60.3 mmol). The reaction mixture was stirred at rt for 12 h and quenched with 1N HCl solution. The organic material was extracted with DCM (50 mL X 2) followed by EtOAc (50 mL X 2), and the extracts were washed with a saline, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chomatography (EtOAc/Hex = 1/3) to give the title compound (5.40 g, 96.7%).

MS[M+H] = 372 (M+1)

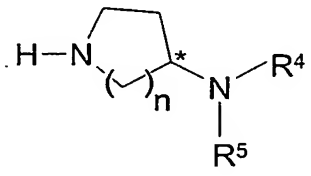
Step B: (3S)-3-[cyclohexyl (isobutyryl)amino]pyrrolidine

To a solution of (3S)-1-cbz-3-[cyclohexyl(isobutyryl)amino]pyrrolidine (5.00 g, 13.4 mmol), prepared in Step A, in Dioxane (40 mL) was added dropwise Pd/C (250 mg) at rt. After 12 h, the reaction mixture was filtered though Celite and the filtrate concentrated *in vacuo* to give the title compound as an oil (3.14 g, 98.5%).

MS[M+H] = 239 (M+1)

Intermediates 37-61.

The compounds below were prepared following the procedure described in Intermediate 36 or a step B of Intermediate 1 using acylchlorides or carbonyl compounds



Intermediates	*	n	R^4	R^5	MS(M+1)
37	S	1	$C(O)C(Me)_3$	c-Hex	253
38	S	1	C(O)Me	c-Hex	227
39	S	1	$S(O)_2Me$	c-Hex	247
40	S	1	$C(O)N(Me)_2$	c-Hex	240
41	S	1	$C(O)CH(Me)_2$	c-Pen	225
42	S	1	$C(O)CH(Me)_2$	c-Hep	253
43	S	1	$C(O)CH(Me)_2$	i-Pr	199
44	S	1	$C(O)CH(Me)_2$	(c-Hex)-CH_2-	253
45	R	1	$C(O)CH(Me)_2$	c-Hex	238
46	R	1	$C(O)C(Me)_3$	c-Hex	253
47	R	1	$C(O)N(Me)_2$	c-Hex	240
48	R	1	$C(O)CH(Me)_2$	c-Pen	225
49		2	$C(O)CH(Me)_2$	c-Hex	253
50		2	$C(O)C(Me)_3$	c-Hex	267
51		2	C(O)OMe	c-Hex	241
52		2	$S(O)_2Me$	c-Hex	261
53		2	$C(O)N(Me)_2$	c-Hex	254
54		2	Et	c-Hex	210
55		2	i-Bu	c-Hex	238
56		2	$C(O)CH(Me)_2$	c-Pen	239
57		2	$C(O)CH(Me)_2$	c-Hep	267
58		2	$C(O)CH(Me)_2$	i-Pr	212
59		2	$C(O)CH(Me)_2$	(c-Hex)-CH_2-	267
60		2	$C(O)CH(Me)_2$	i-Bu	226
61		2	$C(O)N(Me)_2$	2-Me-c-Hex	267

Intermediate 62: (3S)-1-benzyl-3-[(2,4-difluorophenyl)amino]pyrrolidine.

To a solution of (3S)-1-benzyl-3-aminopyrrolidine (0.20 g, 1.1 mmol), tris -(2,4-difluorophenyl)bismuth (0.64 g, 1.2 mmol), and TEA (0.280 mL, 2 mmol) in DCM (5 mL) was added $Cu(OAc)_2$ (0.21 g, 1.2 mmol). After being stirred at rt for 24 h, the

reaction solution was concentrated *in vacuo,* and the residue was purified by column chomatography (MeOH/$CHCl_3$ = 1/25) to give the title compound (150 mg, 46.0%).

MS[M+H] = 289 (M+1)

Intermediate 63: (3S)-1-benzyl-3-[isobutyryl(2,4-difluorophenyl)amino]pyrrolidine.

To a solution of (3S)-1-benzyl-3-[(2,4-difluorophenyl)amino]pyrrolidine (150 mg, 0.52 mmol) and DMAP (6 mg, 0.05 mmol) in pyridine (7 mL) was added isobutyryl chloride (0.16 mL, 1.5 mmol) at 0℃. After being stirred at 60℃ for 18 h, the reaction mixture was quenched with an aqueous $NaH(CO)_3$ solution and extracted with EtOAc. The extracts were concentrated *in vacuo,* the reside was purified by column chomatography (MeOH/$CHCl_3$ = 1/25) to give the title compound (160 mg, 86.0%).

MS[M+H] = 359 (M+1)

Intermediate 64: (3S)-3-[(isobutyryl(2,4-difluorophenyl)amino)pyrrolidine.

To a solution of (3S)-1-benzyl-3-[isobutyryl(2,4-difluorophenyl)amino]pyrrolidine in 1N HCl and an aqueous EtOH solution was added Pd/C, and the reaction mixture was stirred at rt for 3 days under hydrogen. The reaction mixture was filtered though Celite, and the filtrate concentrated *in vacuo*. The crude product was recrystalized from EtOAc to give the title compound (99 mg, 73%) as a colorless prism.

MS[M+H] = 269 (M+1)

Intermediate 65: (3S)-3-[(isobutyryl(2,5-difluorophenyl)amino)pyrrolidine.

The title compound was prepared following the procedure described in Intermediates 63 and 64 using (3S)-1-benzyl-3-[(2,5-difluorophenyl)amino]pyrrolidine.

MS[M+H] = 269 (M+1)

Intermediate 66: (3S)-3-[(isobutyryl(3,4-difluorophenyl)amino)pyrrolidine

The title compound was prepared following the procedure described in Intermediates 63 and 64 using (3S)-1-benzyl-3-[(3,4-difluorophenyl)amino]pyrrolidine.

MS[M+H] = 269 (M+1)

Intermediate 67: 1-hydroxymethyl-1-cyclopentanecarboxylic acid.

Cyclopentanecarboxylic acid (1.10 g, 10.0 mmol) was placed in a round-

bottomed flask, filled with nitrogen, and 30 mL of THF (30 mL) was added. The solution was cooled to -78℃, and LDA (8.8 mL, 2.5 m in hexane) was added dropwise. After being stirred for 30 min., the solution was bubbled by nitrogen stream containing formaldehyde gas (formaldehyde gas was in situ generated by thermal degradation of anhydrouse paraformaldehyde at 160 °C). When the reaction solution turned light yellow, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution at -78℃, and the organic material was extracted with EtOAc. The organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound.

MS[M+H] = 145 (M+1)

Intermediate 68: 2,2-dimethyl-3-methoxypropionic acid.

Step A: 2,2-dimethyl-3-methoxypropionic acid ethyl ester

To a solution of 2,2-dimethyl-3-hydroxypropionic acid ethyl ester (1.3 g, 10.0 mmol) in CH_3CN (30 mL) was added Ag_2O (11.5 g, 50.0 mmol) and methyl iodide (0.56 mL, 11 mmol). The reaction mixture was stirred at rt for 12 h and quenched with a saturated aqueous NH_4Cl. The mixture was filtered though Celite, the filtrate concentrated *in vacuo*, and the residue was purified by column chromatography (EtOAc/Hex = 1/10) to give the title compound (1.34 g, 91.2%).

MS[M+H] = 147 (M+1)

Step B: 2,2-dimethyl-3-methoxypropionic acid.

To a solution of 2,2-dimethyl-3-methoxypropionic acid ethyl ester (1.17 g, 8.00 mmol) in an aqueous MeOH solution ($MeOH/H_2O$ = 1/1, 24 mL) was added LiOH (560 mg, 16.0 mmol) at rt. After the rection mixture was stirred for 30 min., the solvent was removed in vacuo, and the residue was diluted with 1N HCl and EtOAc. The organic layer extracted with EtOAc, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was used without further purification.

MS[M+H] = 133 (M+1)

Intermediate 69: 2,2-dimethyl-3-benzyloxypropionic acid

The title compound was prepared following the procedure described in Intermediate 68 using 2,2-dimethyl-3-hydroxypropionic acid ethyl ester and benzyl chloride.

MS[M+H] = 209 (M+1)

Intermediate 70:1-BOC-piperidine-4-carboxylic acid.

To a solution of piperidine-4-carboxylic acid (1.29 g, 10.0 mmol) in water was added NaOH (800 mg, 20.0 mmol). When the reaction solution was clear, $(BOC)_2O$ (2.5 g, 11.0 mmol) was added, and the reaction mixture was stirred at rt for 12 h. The solvent was removed *in vacuo*, and the residue was diluted with 1N HCl and EtOAc. The organic layer was extracted with EtOAc, and the organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was used without further purification.

MS[M+H] = 230 (M+1)

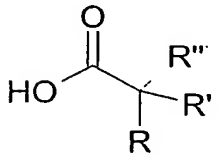
Intermediate 71: (2R)-2-methyl-3-acetyloxypropionic acid.

To a solution of (2R)-2-methyl-3-hydroxypropionic acid (10.0 g, 100 mmol) in pyridine (30 mL) as added acetyl chloride(11.8 g, 15.0 mmol) at 0℃, and the reaction mixture was warmed to rt. After being stirried for 3 h, the reaction mixture was quenched with 1N HCl (30 mL), and the pH of the solution was adjusted to 3-4. The organic material was extracted with EtOAc, and the extracts were washed with 1N HCl at 4-5 times, dried over $MgSO_4$, filtered, and concentrated to give the title compound (11.4 g, 95.0%).

MS[M+H] = 147 (M+1)

Intermediates 72-80.

The compounds below were prepared following the procedure described in Intermediate 67 or 71 using various hydroxy carboxylic acid compounds.



Intermediate	R	R'	R"	MS(M+1)
72	Me	Me	OAc	147
73	Me	Me	CH_2OAc	161
74	Me	Me	$(CH_2)_2OAc$	175
75	Me	Me	$(CH_2)_3OAc$	189
76	Me	CH_2-OAc	CH_2OAc	218
77	$-(CH_2)_3-$		CH_2OAc	187

78	$-(CH_2)_2-$	CH_2OAc	159
79	2-($AcOCH_2$)-1-cyclopenten-1-yl		185
80	2-($AcOCH_2$)-1-cyclohexen-1-yl		199

Intermediate 81: (3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine.

Step A: 2,2-dimethyl-3-acetyloxypropionyl chloride

Intermediate 73, 2,2-dimethyl-3-acetyloxypropionic acid (11.76 g, 80 mmol) was dissolved in benzene (100 mL), and the reaction solution was cooled to 0℃. Oxalyl chloride (15.0 g, 120 mmol) was added dropwise. After being stirred for 3 h, the solvent was removed *in vacuo*, and the residue was distilled *in vacuo* to give the title compound.

MS[M+H] = 179 (M+1)

Step B: (3S)-1-Cbz-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine

To the mixture of (3S)-1-Cbz-3-(cyclohexylamino)pyrrolidine (3.0 g, 10 mmol), TEA (15 mL), and DMAP (1.25 g, 10 mmol) in THF (15 mL) was added 2,2-dimethyl-3-acetyloxypropionyl chloride (3.58 g, 20 mmol) prepared in Step A. After the reaction mixture was refluxed for 48h (90 – 110 ℃), the solvent was removed, and the residue was diluted with an aqueous $NaHCO_3$ solution was added to the residue. The organic material was extracted with EtOAc, and the extracts were washed by 1N HCl, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chomatography (EtOAc/Hex = 1/2) to give the title compound (2.80 g, 62.9%).

MS[M+H] = 445 (M+1)

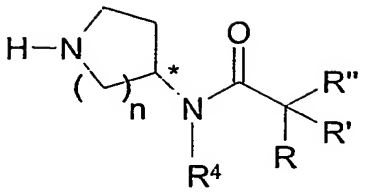
Step C: (3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine

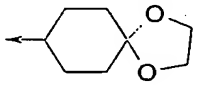
To a solution of (3S)-1-Cbz-3-[cyclohexyl (acetyloxypivaloyl)amino]pyrrolidine (1.00 g, 2.25 mmol), prepared in Step B, in dioxane (10 mL) was added portionwise Pd/C (200 mg), and the mixture was stirred for 12 h under hydrogen. The reaction solution was filtered though Celite and the filtratae concentrated to give the title compound (657 mg, 84%).

MS[M+H] = 311 (M+1)

Intermediates 82~125.

The compounds below were prepared following the procedure described in Intermediate 81 or Step B of Intermediate 1 using commercially available carboxylic acid or carboxylic acid prepared in Intermediates 67~80, and amine compounds prepared in Intermediates 2, 6 and 6~35.



Intermediate	n	*	R	R'	R"	R^4	MS(M+1)
82	1	S	H	OH	i-Pr	c-Hex	311
83	1	S	H	H	$C(Me)_2OH$	c-Hex	269
84	1	S	H	Me	CH_2-OAc	c-Hex	297
85	1	S	Me	Me	OAc	c-Hex	297
86	1	S	Me	Me	$(CH_2)_2$-OAc	c-Hex	325
87	1	S	Me	Me	$(CH_2)_3$-OAc	c-Hex	339
88	1	S	Me	Me	CH_2-OAc	4-*cis*-Me-c-Hex	325
89	1	S	Me	Me	CH_2-OAc	4-*trans*-Me-(c-Hex)	325
90	1	S	Me	Me	CH_2-OAc	4,4-di-Me-(c-Hex)	339
91	1	S	Me	Me	CH_2-OAc	4-t-Bu-(c-Hex)	367
92	1	S	Me	Me	CH_2-OAc	4-*cis*-Et-(c-Hex)	339
93	1	S	Me	Me	CH_2-OAc	4-*trans*-Et-(c-Hex)	339
94	1	S	Me	Me	CH_2-OAc	Spiro[2.5]octan-1-yl	337
95	1	S	Me	Me	CH_2-OAc	4-Ph-c-Hex	387
96	1	S	Me	Me	CH_2-OAc		369
97	1	S	Me	CH_2-OAc	CH_2-OAc	4-*cis*-Me-(c-Hex)	383
98	1	S	Me	CH_2-OAc	CH_2-OAc	4-*trans*-Me-(c-Hex)	383
99	1	S	Me	CH_2-OAc	CH_2-OAc	4,4-di-Me-(c-Hex)	397
100	1	S	Me	CH_2-OAc	CH_2-OAc	c-Hex	369
101	1	S	Me	Me	CH_2-OMe	c-Hex	283
102		S	Me	Me	CH_2-OBn	c-Hex	359
103	1	S	Me	Me	$(CH_2)_3$-O-(2,4-diMe)Ph	c-Hex	401
104	1	S	-$(CH_2)_4$-		CH_2-OAc	c-Hex	337
105	1	S	-$(CH_2)_2$-		CH_2-OAc	c-Hex	309
106	1	S	-$(CH_2)_2$-		CO_2Et	c-Hex	309
107	1	S	H	1-BOC-Pid-4-yl		c-Hex	380
108	1	S	H	1-(Nos)-Pid-4-yl		c-Hex	465
109	1	S	3-OH-Ph			c-Hex	289

110	1	S	2-(AcOCH$_2$)-1-cyclopenten-1-yl			c-Hex	335
111	1	S	2-(AcOCH$_2$)-1-cyclohexen-1-yl			c-Hex	349
112	1	R	Me	Me	CH$_2$-OAc	c-Hex	311
113	1	R,S	Me	Me	CH$_2$-OAc	c-Hex	311
114	1	S	Me	Me	CH$_2$-OAc	2,3-diF-Ph	341
115	1	R,S	Me	Me	CH$_2$-OAc	2,3-diF-Ph	341
116	1	R,S	Me	Me	CH$_2$-OAc	3,5-diMe-ph	333
117	1	R,S	Me	Me	CH$_2$-OAc	4-Me-Ph	319
118	1	R,S	Me	Me	CH$_2$-OAc	Ph	305
119	1	S	Me	Me	CH$_2$-OAc	2-Adamantyl	363
120	2	S	Me	CH$_2$-OAc	CH$_2$-OAc	4-*cis*-Me-(c-Hex)	397
121	2	S	Me	CH$_2$-OAc	CH$_2$-OAc	4-*trans*-Me-(c-Hex)	397
122	2	S	Me	CH$_2$-OAc	CH$_2$-OAc	4,4-di-Me-(c-Hex)	411
123	2	S	Me	Me	CH$_2$-OAc	c-Hex	325
124	2	S	2-(AcOCH$_2$)-1-cyclopenten-1-yl			c-Hex	349
125	2	S	2-(AcOCH$_2$)-1-cyclohexen-1-yl			c-Hex	363

Intermediate 126: (3S)-3-[acetyloxypivaloyl(4,4-diF-cyclohexyl)amino]pyrrolidine.

Step A: (3S)-1-cbz-3-[acetyloxypivaloyl (4-oxo-cyclohexyl)amino]pyrrolidine

Intermediate 96, (3S)-1-cbz-3-[acetyloxypivaloyl(4,4-ethyleneketal-cyclohexyl)amino]pyrrolidine (1.86 g, 5.16mmol) was dissolved in THF (5 mL), and 3N HCl (5 mL) was added. The reaction solution was stirred at 50 °C for 12 h and neutralized by addition of a saturated aqueous 1N NaOH solution. The organic material was extracted with EtOAc and the extracts were dried over $MgSO_4$, concentrated *in vacuo*, and purified by column chomatography (EtOAc/Hex = 1/1) to give the title compound (1.40 g, 85.7%).

MS[M+H] = 459 (M+1)

Step B: (3S)-1-cbz-3-[acetyloxypivaloyl(4,4-difluoro-cyclohexyl)amino]pyrrolidine

The product of Step A, (3S)-1-cbz-3-[acetyloxypivaloyl(4-oxo-cyclohexyl)amino]pyrrolidine (1.40 g, 4.42 mmol) was dissolved in DCM (15 mL), and DAST (1.42 g, 8.84 mmol) was added at –78 °C, and the reaction mixture was warmed to rt . After being stirred for 24 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution w and extracted with DCM. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue purified by column chomatography (EtOAc/Hex = 2/1) to give the title compound (500 mg, 33.5%).

MS[M+H] = 481 (M+1)

Step C: 3-[acetyloxypivaloyl(4,4-diF-cyclohexyl)amino]pyrrolidine

The title compound was prepared following the procedure described in Intermediate 64 using the product of Step B, (3S)-1-cbz-3-[acetyloxypivaloyl (4,4-diF-cyclohexyl)amino]pyrrolidine.

MS[M+1] = 347 (M+1)

Intermediate 127: (3S)-3-[acetyloxypivaloyl(4-F-cyclohexyl)amino]pyrrolidine.

Step A: (3S)-1-cbz-3-[acetyloxypivaloyl(4-hydroxycyclohexyl)amino]pyrrolidine

The product of Step A of Intermediate 126, (3S)-1-cbz-3-[acetyloxypivaloyl (4-oxo-cyclohexyl)amino]pyrrolidine (1.60 g, 3.49 mmol) was dissolved in THF (15 mL), and $NaBH_4$ (172 mg, 4.19 mmol) was added at rt. After being stirred for 12 h, the reaction mixture was quenched with water, and the organic material was extracted with EtOAc. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chomatography (EtOAc/Hex = 1/1) to give the title compound (1.481 mg, 92.1%).

MS[M+H] = 461 (M+1)

Step B: (3S)-1-cbz-3-[acetyloxypivaloyl(4-fluorocyclohexyl)amino]pyrrolidine

The title compound was prepared following the procedure described in Step B of Intermediate 126 using the product of Step A, (3S)-1-cbz-3-[acetyloxypivaloyl(4-hydroxy-cyclohexyl)amino]pyrrolidine.

MS[M+H] = 463 (M+1)

Step C: (3S)-3-[acetyloxypivaloyl(4-fluorocyclohexyl)amino]pyrrolidine

The title compound was prepared following the procedure described in Intermediate 64 using the product of Step B, (3S)-1-cbz-3-[acetyloxypivaloyl(4-fluoro-cyclohexyl)amino]pyrrolidine.

MS[M+1] = 329 (M+1)

Intermediate 128: methyl 2-[(3S)-3-pyrrolidinyl(cyclohexyl)amino]acetate.

Step A: methyl 2-[(3S)-1-Cbz-3-pyrolidinyl(cyclohexyl)amino]acetate

NaH (60% in mineral oil, 52.0 mg, 1.30 mmol) was placed in a round-bottom flask, filled with nitrogen, and then THF (10 mL) was added. A solution of (3S)-1-Cbz-3-(cyclohexylamino)pyrrolidine (302 mg, 1.00 mmol) prepared in Intermediate 2 in

THF was added dropwise at 0℃, and the reaction mixture was stirred for 30 min until no further gas evolution occurred, followed by slow addition of methyl bromoacetate. After 4h, the reaction mixture was quenched with water and extracted with EtOAc. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chomatography (EtOAc/Hex = 1/2) to give the title compound (227 mg, 90.0%).

MS[M+H] = 375 (M+1)

Step B: methyl 2-[(3S)-3-pyrrolidinyl(cyclohexyl)amino]acetate

The title compound was prepared following the procedure described in Step B of Intermediate 3 using the product of Step A, methyl 2-[(3S)-1-Cbz-pyrrolidin-3-yl (cyclohexyl)amino]acetate.

MS[M+H] = 241 (M+1)

Intermediate 129: (3S)-3-{cyclohexyl[(N-BOC)aminoacetyl]amino}pyrrolidine

Step A: A: (3S)-1-Cbz-3-{cyclohexyl[(N-BOC)aminoacetyl]amino}pyrrolidine

To a solution of (3S)-1-Cbz-3-{cyclohexylamino}pyrrolidine (3.0 g, 10.0 mmol), prepared in Intermediate 2, in DMF (30 mL) were added DIPEA (3.50 mL, 20.0 mmol), HBTU (4.88 g, 13 mmol), BOC-Gly (1.92 g, 11 mmol). After the mixture was stirred at rt for 4h, the solvent was removed *in vacuo*, and the residue was diluted with an aqueous $NaHCO_3$. The organic material was extracted with EtOAc, and the organic extracts were washed with 1N HCl, dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified by column chomatography (EtOAc/Hex = 1/3) to give the title compound (4.63 g, 92.0%).

MS[M+H] = 474 (M+1)

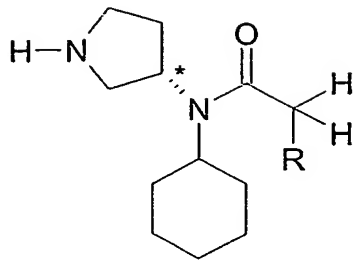
Step B: (3S)-3-{cyclohexyl[(N-BOC)aminoacetyl]amino}pyrrolidine

The title compound was prepared following the procedure described in Step B of Intermediate 3 using the product of Step A, (3S)-1-Cbz-3-{cyclohexyl[(N-BOC)aminoacetyl]amino}pyrrolidine.

MS[M+H] = 340 (M+1)

Intermediates 130~134.

The compounds below were prepared following the procedure described in Intermediate 36 or 129 using commercially available carboxylic acid and amine compounds prepared in Intermediates 6~35.



Intermediate	R	MS(M+1)
130	$CH_2NH(BOC)$	354
131	$CH_2CH_2NH(BOC)$	368
132	$CH_2C(O)OMe$	297
133	CH_2OH	255
134	$(CH_2)_2$-OC(O)-CF_3	365

Intermediate 135: (2R)-N-methanesulfonyl-(4-chlorophenyl)alanine

Step A: (2R)-N-methanesulfonyl-(4-chlorophenyl)alanine methyl ester

To a solution of (2R)-4-chlorophenylalanine methylester (213 mg, 1.00 mmol) in DCM (5 mL) was added dropwise TEA (280 ㎕, 2.00 mmol) and then methanesulfonylchloride (100 ㎕, 1.3 mmol) at 0℃. After 30 min, the reaction mixture was quenched with water and extracted with DCM and EtOAc. The organic solution was washed with 1N HCl, dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chomatography ($MeOH/CHCl_3$ = 1/25) to give the title compound (280 mg, 96.1%).

MS[M+H] = 292 (M+1)

Step B: (2R)-N-methanesulfonyl-(4-chlorophenyl)alanine

To a solution of (2R)-N-methanesulfonyl-(4-chlorophenyl)alanine methylester, prepared in Step A, in water/methanol (5 mL, 1/1) was added portionwise LiOH (70.0 mg, 2.00 mmol). After being stirred at rt for 3 h, the reaction mixture was concentrated, and the residue was diluted with 1N HCl solution. The organic material was extracted with EtOAc, the extracts were concentrated *in vacuo* to give the title compound (179 mg, 94.3%).

MS[M+H] = 277 (M+1)

Intermediate 136: (2R)-N-acetyl-(4-chlorobenzyl)alanine

The title compound was prepared following the procedure described in Intermediate 135 using anhydrous (2R)-4-chlorophenylalanine methylester.

MS[M+H] = 278 (M+1)

Intermediate 137: (2R)-N-[(N,N-dimethyl)carbamoyl]-(4-chlorobenzyl)alanine

The title compound was prepared following the procedure described in Intermediate 135 using (2R)-4-chlorophenylalanine methylester and chlorodimethyl carbamate.

MS[M+H] = 278 (M+1)

Intermediate 138: (2R)-N-BOC-prolinal

Step A: (2R)-N-BOC-proline ethylthioester

To a solution of DCC (2.55 g, 12.4 mmol), DMAP (100 mg), and EtSH (0.71 g, 11.1 mmol) in DCM was added dropwise a solution of (2R)-N-BOC-proline (3.00 g, 9.52 mmol) in DCM (30 mL). The reaction mixture was stirred at rt for 30 min, and filtered though Celite. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chomatography (EtOAc/Hex = 1/4) to give the title compound (2.34 g, 95.2%).

MS[M+H] = 260 (M+1)

Step B: (2R)-N-BOC-prolinal

To a solution of (2R)-N-BOC-proline ethylthioester, prepared in Step A, in acetone were added dropwise triethylsilane (5.39 g, 46.3 mmol) and Pd/C (100 mg) at 0℃. When no further gas evolution occurred, the reaction mixture was warmed to rt and then stirred for additional 30 min. The reaction solution was filtered though Celite, the filtrate concentrated *in vacuo*. The residue was purified by column chomatography (EtOAc/Hex = 1/2) to give the title compound (1.43 g, 93.2%).

MS[M+H] = 200 (M+1)

Intermediate 138: (2R)-N-methylprolinal

Step A: (2R)-N-methylproline methyl ester

(2R)-proline methylester (1.20 g, 10.0 mmol) was dissolve in DMF (30 mL), and formalin (37% in water, 1.12 mL, 15.0 mmol) and $NaBH(OAc)_3$ (4.20 g, 20.0 mmol) were added portionwise. After 12h, the reaction material was concentrated *in vacuo*, and the residue was diluted with $NaHCO_3$ (30 mL). The organic material was

extracted with EtOAc, and the organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chomatography (EtOAc/Hex = 4/1) to give the title compound (1.33 g, 93.0%).

MS[M+H] = 144 (M+1)

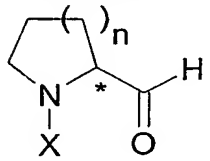
Step B: (2R)-N-methylprolinal

The title compound was prepared following the procedure described in Step of Intermediate 135 using methyl (2R)-N-methyl-proline methylester prepared in Step A.

MS[M+H] = 114 (M+1)

Intermediates 140~148.

The compounds below were prepared following the procedure described in Intermediates 138 and 139 using various amino acid derivatives.



Intermediate	X	n	*	MS(M+1)
140	Me	1	S	114
141	Ac	1	R	142
142	$S(O)_2Me$	1	R	178
143	$C(O)N(Me)_2$	1	R	171
144	n-Bu	1	R	156
145	Me	2	S	128
146	Me	2	R	128
147	Ac	2	R	156
148	$S(O)_2Me$	2	R	192

Intermediate 149: 1-BOC-2-aziridinecarboxylic acid

Step A: Methyl 1-benzyl-2-aziridinecarboxylate

To a solution of methyl 2,3-dibromopropionate (92.50 g, 10.0 mmol) and K_2CO_3 (4.10 g, 30.0 mmol) in acetonitrile (30 mL) was added dropwise benzylamine (1.20 mL, 11 mmol). After being stirred at rt for 4 h, and the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The organic material was extracted with EtOAc, the extracts dried over $MgSO_4$, concentrated *in vacuo*. The residue was

purified by column chomatography (EtOAc/Hex = 2/1) to give the title compound (1.62 g, 85%).

MS[M+H] = 192 (M+1)

Step b: Methyl 1-BOC-2-aziridine carboxylate

To a solution of methyl 1-benzyl-2-aziridinecarboxylate (1.00 g, 5.23 mmol) and di-t-butyl-dicarbonate (1.34 g, 5.75 mmol), prepared in Step A, in methanol (20 mL) was added portionwise Pd/C (300 mg). The mixture was stirred at rt under hydrogen for 24 h and filtered though Celite. The filtrate was concentrated *in vacuo,* and the residue was purified by column chomatography (EtOAc/Hex = 2/1) to give the title compound (985 mg, 91.0%).

MS[M+H] = 202 (M+1)

Step C: 1-BOC-aziridine-2-carboxylic acid

The title compound was prepared following the procedure described in Step B of Intermediate 135 using methyl 1-BOC-2-aziridinecarboxylate prepared in Step B.

MS[M+H] = 188 (M+1)

Intermediate 150: 1-BOC-aziridine-2-carboxaldehyde

The title compound was prepared following the procedure described in Intermediate 138 using 1-BOC-aziridine-2-carboxylic acid.

MS[M+H] = 172(M+1)

Intermediate 151: 2-ethylamino-1-acetyloxyethane

Step A: 2-(BOC)amino-1-acetyloxyethane

To a solution of 2-(BOC)aminoethanol (3.2 g, 20.0 mmol) in DCM (60 mL) were added TEA (5.6 mL, 40.0 mL) and acetyl chloride (3.36 mL, 30 mmol) at 0℃. After the reaction solution was stirred for 2 h, the solvent was removed, and the residue dissolved in water. The organic material was extracted with EtOAc, and the extracts were washed with 1N HCl, dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified by column chomatography (eluent: EtOAc/Hex = 1/10) to give the title compound (3.2 g, 80%).

MS[M+H] = 204(M+1)

Step B: 2-amino-1-acetyloxyethane

2-(BOC)amino-1-acetyloxyethane (3.00 g, 15.0 mmol), prepared in Step A,

was dissolved in DCM (15.0 mL), and TFA (15.0 mL) was added. After being stirred 30 min, the reaction mixture was concentrated *in vacuo* to give the title compound. The product was used without further purification.

MS[M+H] = 104(M+1)

Step C: 2-[(2-nitrobenzene)sulfonyl]amino-1-acetyloxyethane

To a solution of 2-amino-1-acetyloxyethane (1.00 g, 10.0 mmol), prepared in Step B (1.00 g, 10.0 mmol) and Et_3N (2.80 mL, 20 mmol) in DCM (30 mL) was added dropwise (2-nitrobenzene)sulfonyl chloride (2.43 g, 22 mmol). After being stirred at rt for 4 h, the reaction mixture was quenched with water and extracted with EtOAc. The extracts were washed with 1N HCl, dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified by column chomatography (eluent: EtOAc/Hex = 1/3) to give the title compound (2.72 g, 94.0%).

MS[M+1] = 289(M+1)

Step D: 2-{ethyl[(2-nitrobenzene)sulfonyl]}amino-1-acetyloxyethane

To a solution of 2-[(2-nitrobenzene)sulfonyl]amino-1-acetyloxyethane prepared in Step C (1.45 g, 5.00 mmol) and $P(Ph)_3$ (1.3 g, 5 mmol) in THF (15 mL) were added ethanol (0.40 mL, 15 mmol) and DEAD (0.32 mL, 10.0 mmol). After being stirred for 12 h, the solvent was removed and the residue was purified by column chromatography (eluent: EtOAc/Hex = 1/5) to give the title compound (1.40 g, 80%).

MS[M+1] = 317(M+1)

Step E: 2-ethylyamino-1-acetyloxyethane

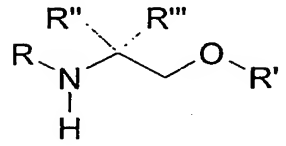
To a solution of 2-{ethyl[(2-nitrobenzene)sulfonyl]}amino-1-acetyloxyethane (634 mg, 2.00 mmol) prepared in Step D in DMF (10 mL) were added K_2CO_3 (540 mg, 4 mmol) and mercaptobenzene (330 mg, 1.5 mmol). The reaction mixture was stirred at rt for 1 h, concentrated *in vacuo*, and diluted with water. The organic material was extracted with EtOAc; and the extracts were washed with 1N HCl, dried over $MgSO_4$, concentrated *in vacuo*. The residue was purified by column chomatography (eluent: EtOAc/Hex = 1/3) to give the title compound.

MS[M+H] = 132(M+1)

Intermediate 152-157:

The compounds below were prepared following the procedure described in Intermediates 151 using commercially available aminoalcohol or (N-

BOC)aminoethanol.



Intermediate	R	R'	R"	R"'	MS(M+1)
152	Pr	Ac	H	H	146
153	Et	Me	H	H	104
154	c-Pr	Ac	H	H	144
155	CH_2CH_2OMe	Ac	H	H	162
156	Me	Ac	Me	Me	146
157	CH_2CH_2OMe	Me	H	H	134

Intermediate 158: (2R)-2-(BOC)amino-N-{4-[cyclohexyl(hydroxyethylcarbamoyl)amino]piperidine-1-yl}-3-(4-chlorophenyl)propionamide

Step A: 4-[(cyclohexyl)amino]piperidine

The title compound was prepared following the procedure described in Step A of Intermediate 1 using 1-BOC-4-[(cyclohexyl)amino]piperidine prepared in Intermediate 26.

MS[M+H] = 183(M+1)

Step B: (2R)-2-(BOC)amino-N-[4-(cyclohexylamino)piperidine-1-yl]-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Intermediate 129 using (2R)-2-(BOC)amino-3-(4-chlorophenyl)propionic acid and 4-[(cyclohexyl)amino]piperidine.

MS[M+H] = 464(M+1)

Step C: N-cyclohexyl[(2R)-2-(BOC)amino-3-(4-chlorophenyl)-1-oxo]piperidine-4-yl}carbamoyl chloride.

To a solution of (2R)-2-(BOC)amino-N-[4-(cyclohexylamino)poperidine-1-yl]-3-(4-chlorophenyl)propionamide prepared in Step B (4.63g, 10 mmol) in DCM (30 mL) was added phosgene (25% in toluene, 12.6 mL, 30 mmol). After the reaction solution

was stirred at rt for 4 h, the solvent was removed, and the residue was purified by column chomatography (eluent: EtOAc/Hex = 1/3) to give the title compound (4.58 g, 87%).

MS[M+H] = 526(M+1)

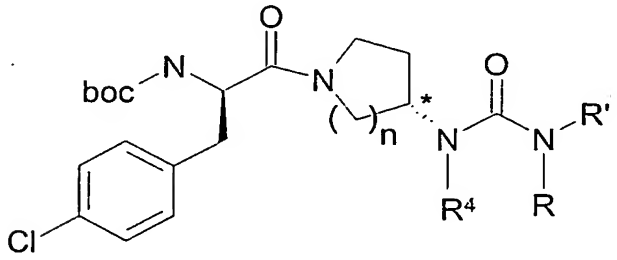
Step D: (2R)-2-(BOC)amino-N-{(4-[cyclohexyl(hydroxyethylcarbamoyl)amino]piperidine-1-yl)-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step B of Intermediate 81 using N-cyclohexyl[(2R)-2-(BOC)amino-3-(4-chlorophenyl)-1-oxo]piperidine-4-yl}carbamoyl chloride.

MS[M+H] = 551(M+1)

Intermediate 159-190:

The compounds below were prepared following the procedure described in Intermediates 158 using commercially available aminoalcohols or amine compounds prepared in Intermediate 6-35.



Intermediate	R	R'	R^4	n	*	MS(M+1)
159	H	$CH_2(CH_2)_3NH(BOC)$	c-Hex	1	S	664
160	H	$CH_2(CH_2)_2NH(BOC)$	c-Hex	1	S	650
161	H	$CH_2CH_2NH(BOC)$	c-Hex	1	S	636
162	H	CH_2CH_2OH	c-Hex	1	S	537
163	CH_2CH_2OH	CH_2CH_2OH	c-Hex	1	S	581
164	H	CH_2CH_2OMe	c-Hex	1	S	551
165	3(S)-hydroxy-Pyd-1-yl		c-Hex	1	S	563
166	2(S)-hydroxymethyl-Pyd-1-yl		c-Hex	1	S	577

167	Me	CH_2CH_2OH	c-Hex	2		565
168	Et	CH_2CH_2OH	c-Hex	2		579
169	Pr	CH_2CH_2OH	c-Hex	2		593
170	c-Pr	CH_2CH_2OH	c-Hex	2		591
171	CH_2CH_2OMe	CH_2CH_2OH	c-Hex	2		609
172	Me	CH_2CH_2OMe	c-Hex	2		579
173	Et	CH_2CH_2OMe	c-Hex	2		593
174	CH_2CH_2OMe	CH_2CH_2OMe	c-Hex	2		623
175	Me	Et	c-Hex	2		563
176	Me	OMe	c-Hex	2		551
177	Me	$C(Me)_2CH_2OH$	c-Hex	2		593
178	Me	CH_2CH_2OH	2,3-diF-Ph	2		593
179	Me	CH_2CH_2OMe	2,3-diF-Ph	2		609
180	CH_2CH_2F	CH_2CH_2OMe	c-Hex	2		611
181	3(R)-hydroxy-Pyd-1-yl		c-Hex	2		577
182	3(S)-hydroxy-Pyd-1-yl		c-Hex	2		577
183	(2R)-hydroxymethyl-Pyd-1-yl		c-Hex	2		591
184	(2S)-hydroxymethyl-Pyd-1-yl		c-Hex	2		591
185	(3S)-N-BOC-amino-Pyd-1-yl		c-Hex	2		576
186	(3R)-N-BOC-amino-Pyd-1-yl		c-Hex	2		576
187	(3R)-hydroxy-Pid-1-yl		c-Hex	2		591
188	(3S)-hydroxy-Pid-1-yl		c-Hex	2		591
189	4-hydroxy-Pid-1-yl		c-Hex	2		591
190	4-N-BOC-amino-Pid-1-yl		c-Hex	2		590

Intermediate 191: 4-[cyclohexyl(isopropylcarbamoyl)amino]piperidine

Step A: 1-BOC-4-[cyclohexyl(isopropylcarbamoyl)amino]piperidine

To a solution of 1-BOC-4-(cyclohexylamino)piperidine (282 mg, 1.00 mmol) in DCM(3 mL) was added isopropyl isocyanate (108 $\mu\ell$, 1.10 mmol). After being stirred at rt for 30 min, the reaction solution was concentrated *in vacuo*, and the residue was purified by column chomatography (eluent: EtOAc/Hex = 1/5) to give the title compound (354 mg, 94.0%).

MS[M+H] = 368(M+1)

Step B: 4-[cyclohexyl(N-isopropylcarbamoyl)amino]piperidine

The title compound was prepared following the procedure described in Step B of Intermediate 1 using 1-BOC-4-[cyclohexyl(N-isopropylcarbamoyl)amino]piperidine.

MS[M+H] = 268(M+1)

Intermediate 192: 4-{cyclohexyl[methyl(isopropyl)carbamoyl]amino}piperidine

Step A: 1-BOC-4-{cyclohexyl[methyl(isopropyl)carbamoyl]amino}piperidine

The title compound was prepared following the procedure described in Step A of Intermediate 128 using 1-BOC-4-[cyclohexyl(isopropylcarbamoyl)amino]piperidine.

MS[M+H] = 382(M+1)

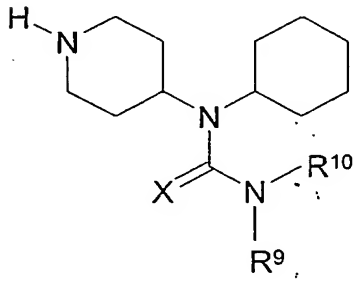
Step B: 4-{cyclohexyl[methyl(isopropyl)carbamoyl]amino}piperidine

The title compound was prepared following the procedure described in Step B of Intermediate 1 using 1-BOC-4-{cyclohexyl[methyl(isopropyl)carbamoyl]amino}piperidine.

MS[M+H] = 282(M+1)

Intermediate 193-198:

The compounds below were prepared following the procedure described in Intermediates 128 or Step A of Intermediate 191 using 1-BOC-4-(cyclohexylamino)piperidine and isocyanates or isothiocyanates.



Intermediate	X	R^9	R^{10}	MS(M+1)
193	O	H	n-Bu	281
194	O	H	c-Hex	307
195	O	H	Ph	301
196	O	Me	n-Bu	295
197	S	H	Et	275
198	S	Me	Et	289

Intermediate 199: methyl [cyclohexyl(piperidin-4-yl)amino]acetate

Step A: methyl {cyclohexyl[1-(BOC)piperidin-4-yl]amino}acetate

The title compound was prepared following the procedure described in Step A of Intermediate 128 using 1-BOC-4-(cyclohexylamino)poperidine.

MS[M+H] = 355(M+1)

Step B: methyl [cyclohexyl(piperidin-4-yl)amino]acetate

The title compound was prepared following the procedure described in Step B of Intermediate 1 using methyl {cyclohexyl[1-(BOC)piperidin-4-yl]amino}acetate prepared in Step A.

MS[M+H] = 255(M+1)

Intermediate 200: (2R)-2-(BOC)amino-N-(3-hydroxyazetidine-1-yl)-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Intermediate 129 using (2R)-1-BOC-(4-chlorophenyl)alanine and 3-hydroxyazetidine (*Syn. Lett.*, **1991**, 783.).

MS[M+H] = 355(M+1)

Intermediate 201: (2R)-2-(BOC)amino-N-(3-oxo-azetidine-1-yl)-3-(4-chlorophenyl)propionamide

(2R)-2-(BOC)Amino-N-(3-hydroxyazetidine-1-yl)-3-(4-chlorophenyl)propionamide (3.54 g, 10 mmol) was placed in a round-bottomed flask, filled with nitrogen, and DCM (30 mL) and oxalyl chloride (872 $\mu\ell$, 10 mmol) were

added. The mixture was cooled to -78℃, and DMSO (709 $\mu\ell$, 10 mmol) was added. The reaction solution was stirred for 3 h keeping the temperature below –50 °C. The reaction mixture was quenched by addition of TEA and warmed to rt. The reaction solution was diluted with a saturated aqueous NH_4Cl solution, and the organic material was extracted with EtOAc. The extracts was dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chomatography (eluent: EtOAc/Hex = 1/3) to give the title compound (2.88 g, 84%).

MS[M+H] = 353(M+1)

Intermediate 202: (2R)-2-(BOC)amino-N-[3-(cyclohexylamino)azetidine-1-yl]-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Intermediate 2 using (2R)-2-(BOC-amino)-N-(3-oxo-azetidine-1-yl)-3-(4-chlorophenyl)propionamide prepared in Intermediate 201 and cyclohexylamines.

MS[M+H] = 437(M+1)

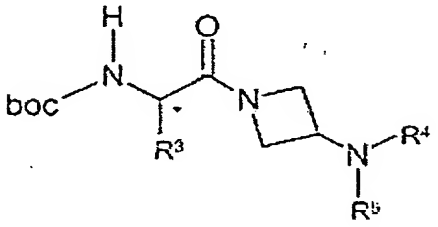
Intermediate 203: (2R)-2-(BOC)amino-N-{3-[cyclohexyl(isobutyryl)amino]azetidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Intermediate 36 using (2R)-2-(BOC)amino-N-[3-(cyclohexylamino)azetidine-1-yl]-3-(4-chlorophenyl)propionamide prepared in Intermediate 202 and isobutyrylchloride.

MS[M+H] = 507(M+1)

Intermediate 204-217:

The compounds below were prepared following the procedure described in Intermediates 201 and 203 using (2R)-2-(BOC)amino-N-(3-hydroxyazetidine-1-yl)-3-(4-chlorophenyl)propionamide prepared in Intermediate 200.



Intermediate	R^3	*	R^4	R^5	MS(M+1)
204	4-Cl-Bn	R	$C(O)C(Me)_3$	c-Hex	520
205	4-Cl-Bn	R	C(O)OMe	c-Hex	494
206	4-Cl-Bn	R	$S(O)_2Me$	c-Hex	515
207	4-Cl-Bn	R	$C(O)N(Me)_2$	c-Hex	507
208	4-Cl-Bn	R	$C(O)CH(Me)_2$	c-Pen	492
209	4-Cl-Bn	R	$C(O)CH(Me)_2$	c-Hep	520
210	4-Cl-Bn	R	$C(O)CH(Me)_2$	i-Pr	466
211	4-Cl-Bn	R	$C(O)CH(Me)_2$	i-Bu	480
212	4-Cl-Bn	R	$C(O)CH(Me)_2$	(c-Hex)-CH_2-	520
213	4-Cl-Bn	R	$C(O)CH(Me)_2$	2-Me-c-Hex	520
214	Bn	R	$C(O)CH(Me)_2$	c-Hex	472
215	Bn	R	$C(O)CH(Me)_2$	c-Hex	486
216	Bn	R	$C(O)C(Me)_3$	c-Hex	500
217	(c-Hex)-CH_2-	R	$C(O)CH(Me)_2$	c-Hex	478

Intermediate 218: (2R)-2-(BOC)amino-N-{3-[cyclohexyl(methoxycarbonyl)amino]azetidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Intermediate 135 using (2R)-2-(BOC)amino-N-[3-(cyclohexylamino)azetidine-1-yl]-3-(4-chlorophenyl)propionamide prepared in Intermediate 202 and methyl bromoacetate.

MS[M+H] = 508(M+1)

The present invention is illustrated by the following examples. However, the scopes of the invention are not limited to these examples.

Examples

Example 1: (2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide · TFA

Step A: (2R)-2-(BOC-amino)-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine (HCl salt, 917 mg, 3.30 mmol) in DMF (30 mL) were added DIPEA (1.15 mL, 6.70 mmol), (2R)-N-BOC-(4-chlorophenyl)alanine (1.00 mg, 3.30 mmol), HOBT (668 mg, 5.00 mmol), and EDC (845 mg, 4.30 mmol). After being stirred at rt for 12 h, the reaction solution was concentrated *in vacuo*, and the residue was diluted with a saturated $NaHCO_3$ solution and EtOAc. The organic layer was extracted with EtOAc and subsequently washed with a saturated aqueous $NaHCO_3$ solution, water and an aqueous 1N HCl solution. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chomatography (eluent: EtOAc/Hex = 1/2) to give the title compound (1.58 g, 93.9%).

MS[M+H] = 520(M+1)

Step B: (2R)-2-amino-N-{(3R)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide · TFA

(2R)-2-(BOC-amino)-N-{(3R)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide, prepared in Step A, (1.00 g, 1.93 mmol) was dissolved in DCM (7 mL), and TFA (7 mL) was added dropwise. After the solution was stirred at rt for 1 h, the solvent was removed *in vacuo*, and the residue was purified by HPLC to give the title compound (TFA salt, 979 mg, 95.1%).

MS [M+H] = 420 (M+1)

Example 2: (2R)-2-{[(2R)-pyrrolidine-2-yl]carbonyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide · 2TFA

Step A: (2R)-2-{[(2R)-1-(BOC)pyrrolidine-2-yl]carbonyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA, prepared in Example 1, (100 mg, 0.188 mmol) in DMF (3 mL) were added DIPEA (66.1 mL, 0.381 mmol), EDC (48.7 mg, 0.252 mmol), HOBT (43.6 mg, 0.322 mmol), and (2R)-N-BOC-proline (40.9 mg, 0.190 mmol). After the reaction mixture was stirred at rt for 12 h, DMF was removed *in vacuo*, and the residue was diluted with a saturated aqueous $NaHCO_3$ solution and EtOAc. The organic layer was extracted with EtOAc and

subsequently washed with a saturated aqueous $NaHCO_3$ solution, water and an aqueous 1N HCl solution. The organic solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chomatography (eluent: EtOAc/Hex = 2/1) to give the title compound (107 g, 90.8%).

MS [M+H] = 617 (M+1)

Step B: (2R)-2-{[(2R)-pyrrolidine-2-yl]carbonyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

To a solution of (2R)-2-{[(2R)-1-(BOC)pyrrolidine-2-yl]carbonyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide, prepared in Step A, (50.0 mg, 0.081 mmol) in DCM (2 mL) was added TFA (2 mL). After the reaction solution was stirred at rt for 30 min. the solvent was removed *in vacuo*, and the residue was purified by HPLC to give the title compound (50.0 mg, 98.2%).

MS[M+H] = 517(M+1)

Example 3: (2R)-2-{[(2R)-pyrrolidine-2-yl]methyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-{[(2R)-1-(BOC)pyrrolidine-2-yl]methyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide, prepared in Example 1, (TFA salt, 100 mg, 0.191 mmol) and (2R)-N-BOC-proline carboxyaldehyde (39.6 mg, 0.2 mmol) in DCE (3 mL) was added and $NaBH(OAc)_3$ (96 mg, 4 mmol) at rt. After being stirred 4 h, the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution, and the organic material was extracted with with DCM followed by EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuó*. The residue was purified by column chomatography (eluent: DCM/MeOH = 9/1) to give the title compound (107 mg, 90.8%).

MS [M+H] = 603 (M+1)

Step B: (2R)-2-{[(2R)-pyrrolidine-2-yl]methyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

To a solution of (2R)-2-{[(2R)-1-(BOC)pyrrolidine-2-yl]methyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-

chlorophenyl)propionamide(50 mg, 0.0831 mmol), prepared in Step A, in DCM (2 mL) was added TFA (2 mL). After being stirred at rt for 1 h, the reaction solution was concentrated *in vacuo*, and the residue was purified by HPLC to give the title compound (58.8 mg, 97.1%).

MS[M+H] = 517(M+1)

Example 4: (2R)-2-{methyl[((2R)-pyrrolidine-2-yl)methyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Example 3 using (2R)-2-{[(2R)-1-(BOC)pyrrolidine-2-yl]methyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step B of Example 3 and formaline.

MS[M+H] = 531(M+1)

Example 5: (2R)-(dimethyl)amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Example 3 using (2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Example 1 and formaline.

MS[M+H] = 449(M+1)

Example 6: (2R)-2-[1-(methyl)azetidine-3-yl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-[1-(BOC)azetidine-3-yl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 3 using (2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Example 1 and BOC-3-oxo-azetidine.

MS[M+H] = 575(M+1)

Step B: (2R)-2-{Fmoc[1-(BOC)azetidine-3-yl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Intermediate 1 using (2R)-2-[1-(BOC)azetidine-3-yl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared Step A.

MS[M+H] = 797(M+1)

Step C: (2R)-2-[Fmoc(azetidine-3-yl)]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step B of Example 1 using (2R)-2-{Fmoc[1-(BOC)azetidine-3-yl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step B

MS[M+H] = 697(M+1)

Step D: (2R)-2-{Fmoc[1-(methyl)azetidine-3-yl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 3 using (2R)-2-[Fmoc(azetidine-3-yl)]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared Step C.

MS[M+H] = 711(M+1)

Step E: (2R)-2-[1-(methyl)azetidine-3-yl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

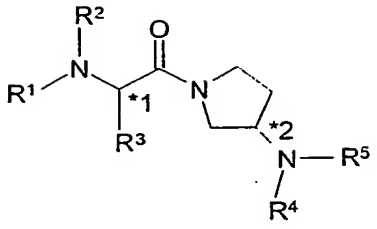
(2R)-2-{Fmoc[1-(methyl)azetidine-3-yl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step D(71.1 mg, 1 mmol) was dissolved in 50% of piperidine-DMF (2 mL). After being stirred 30 min., the reaction mixture was concentrated *in vacuo*, and the residue was purified by HPLC to give the title compound (52 mg, 73.5%).

MS[M+H] = 489(M+1)

Example 7-186:

The compounds below were prepared following the procedure described in Example 1-6 using pyrrolidine, piperidine, or azetidine derivatives prepared in the

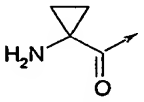
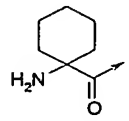
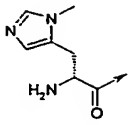
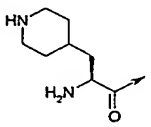
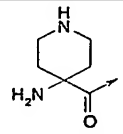
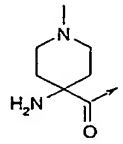
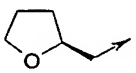
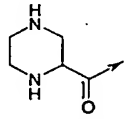
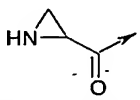
above Intermediates.

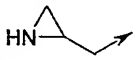
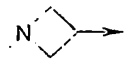


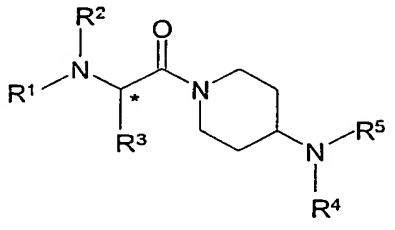
nTFA

Exm.	R^1	R^2	R^3	*1	R^4	*2	R^5	n	MS(M+1)
7	H	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	434
8	H	H	4-Cl-Bn	R	c-Hex	S	C(O)OMe	1	408
9	H	H	4-Cl-Bn	R	c-Hex	S	$C(O)N(Me)_2$	1	421
10	H	H	4-Cl-Bn	R	c-Hex	S	SO_2Me	1	428
11	H	H	4-Cl-Bn	R	c-Hex	S	$CH_2C(O)OMe$	1	422
12	H	H	4-Cl-Bn	R	c-Hex	S	SO_2NH_2	1	429
13	H	H	4-Cl-Bn	R	c-Hex	S	Gly	2	409
14	H	H	4-Cl-Bn	R	c-Hex	S	$CH_2C(O)N(Me)_2$	2	435
15	H	H	4-Cl-Bn	R	c-Hex	S	CH_2SO_2Me	1	442
16	H	H	4-Cl-Bn	R	c-Hex	R	$C(O)CH(Me)_2$	1	420
17	H	H	4-Cl-Bn	R	c-Hex	R	$C(O)C(Me)_3$	1	434
18	H	H	4-Cl-Bn	R	c-Pen	S	$C(O)CH(Me)_2$	1	406
19	H	H	4-Cl-Bn	R	c-Hep	S	$C(O)CH(Me)_2$	1	434
20	H	H	4-Cl-Bn	R	i-Pr	S	$C(O)CH(Me)_2$	1	480
21	H	H	4-Cl-Bn	R	(c-Hex)-CH_2	S	$C(O)CH(Me)_2$	1	434
22	H	H	4-Cl-Bn	R	4,4-diMe-c-Hex	S	$C(O)CH(Me)_2$	1	448
23	H	H	4-Cl-Bn	R	c-Pen	R	$C(O)CH(Me)_2$	1	406
24	H	H	4-Cl-Bn	S	c-Hex	S	$C(O)CH(Me)_2$	1	420
25	H	H	Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	386
26	H	H	4-Br-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	465
27	H	H	4-MeO-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	416
28	H	H	3,4-diCl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	454
29	H	H	4-F-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	404
30	H	H	4-HO-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	402
31	H	H	(c-Hex)-CH_2	R	c-Hex	S	$C(O)CH(Me)_2$	1	392
32	H	H	(indol-2-yl)-CH_2	R	c-Hex	S	$C(O)CH(Me)_2$	2	425
33	H	H	i-Bu	R	c-Hex	S	$C(O)CH(Me)_2$	1	352
34	H	H	$NH_2C(O)CH_2$	R	c-Hex	S	$C(O)CH(Me)_2$	1	353

35	H	H	4-Cl-Bn	R	2,3-diF-Ph	S	$C(O)CH(Me)_2$	1	450
36	H	H	4-Cl-Bn	R	2,4-diF-Ph	S	$C(O)CH(Me)_2$	1	450
37	H	H	4-Cl-Bn	R	2,3-diF-Ph	R	$C(O)CH(Me)_2$	1	450
38	H	H	4-Cl-Bn	R	2,4-diF-Ph	R	$C(O)CH(Me)_2$	1	450
39	Me	Me	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	465
40	Ac	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	462
41	$MeSO_2$	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	498
42	$(Me)_2NC(O)$-CH_2	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	505
43	Gly	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	477
44	$H_2NC(O)$-CH_2	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	477
45	N-diMe-Gly	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	505
46	N-Ac-Gly	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	519
47	N-Ms-Gly	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	555
48	(R)Ala	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	491
49	β-Ala	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	491
50	β-Ala	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	505
51	N-diMe-β-Ala	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	533
52	4-amino-Bu	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	505
53	(S)Ala	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	491
54	(S)His	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	606
55	N-Me-(S)His	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	620
56	N-Ac-(S)His	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	648
57	N-Ac-(S)His	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	662
58	N-Ms-(S)His	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	684
59	(R)His	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	606
60	(S)Phe	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	567
61	(R)Phe	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	567
62	(R)Pro	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	531
63	N-Me-(R)Pro	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	545
64	(S)Pro	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	517
65	(R)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	531
66	(R)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	1	545
67	1-Me-(R)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	545
68	1-Ac-(R)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	573

69	(S)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	531
70	(R)Tic	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	579
71	(R)Tic	H	Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	545
72	(S)Tic	H	4-Cl-Bn	R	c-Hex	R	$C(O)CH(Me)_2$	1	579
73	cis-Dic	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	583
74		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	503
75		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	545
76		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	570
77		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	574
78		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	546
79		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	2	560
80		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	504
81		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	532
82	$HO\text{-}CH_2\text{-}C(O)$	H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	0	478
83		H	4-Cl-Bn	R	c-Hex	S	$C(O)CH(Me)_2$	1	489
84	$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	c-Hex	S	$C(O)C(Me)_3$	2	517
85	$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	c-Hex	R	$C(O)CH(Me)_2$	2	503
86	$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2,3-diF-Ph	R	$C(O)CH(Me)_2$	2	533
87	$(R)Pyd\text{-}2\text{-}CH_2$	H	4-Cl-Bn	R	2,4-DiF-Ph	R	$C(O)CH(Me)_2$	2	533

88	(R)Pyd-2-CH_2	H	4-Cl-Bn	R	c-Pen	S	C(O)CH(Me)$_2$	2	589
89	(R)Pyd-2-CH_2	H	Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	569
90	(R)Pyd-2-CH_2	H	(c-Hex)-CH_2-	R	c-Hex	S	C(O)CH(Me)$_2$	2	475
91	(R)-1-Ac-Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	1	545
92	(S)Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	503
93	(S)Pyd-2-CH_2	Me	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	517
94	(S)-1-Me-Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	517
95	(R)Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	517
96	(R)-1-Me-Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	531
97	(R)-1-Me-Pid-2-CH_2	Me	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	559
98	(S)Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	517
99	(S)-1-Me-Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	531
100		H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	475
101		H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	475
102	1-Me-Pid-4-yl	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	503
103	Pid-4-yl	H	4-Cl-Bn	R	c-Hex	S	C(O)CH(Me)$_2$	2	503
104	Pid-4-yl	Me	4-Cl-Bn	R	c-Hex	S	C(O)C(Me)$_2$	2	517



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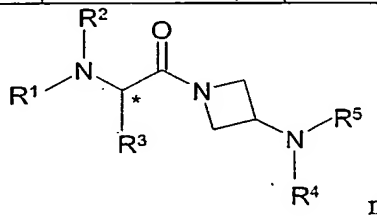
Exm.	R^1	R^2	R^3	*	R^4	R^5	n	MS (M+1)
105	H	H	4-Cl-Bn	R	c-Hex	C(O)CH(Me)$_2$	1	434
106	H	H	4-Cl-Bn	R	c-Hex	C(O)C(Me)$_3$	1	448
107	H	H	4-Cl-Bn	R	c-Hex	C(O)OMe	1	422
108	H	H	4-Cl-Bn	R	c-Hex	C(O)N(Me)$_2$	1	435
109	H	H	4-Cl-Bn	R	c-Hex	CH_2C(O)OMe	2	436
110	H	H	4-Cl-Bn	R	c-Hex	Gly	1	423
111	H	H	4-Cl-Bn	R	c-Hex	CH_2C(O)N(Me)$_2$	2	449
112	H	H	4-Cl-Bn	R	c-Hex	C(O)NH(i-Pr)	1	449
113	H	H	4-Cl-Bn	R	c-Hex	C(O)N(i-Pr)(Me)	1	463

114	H	H	4-Cl-Bn	R	c-Hex	C(O)N(Bu)	1	463
115	H	H	4-Cl-Bn	R	c-Hex	C(O)N(Bu)(Me)	1	477
116	H	H	4-Cl-Bn	R	c-Hex	C(O)N(c-Hex)	1	489
117	H	H	4-Cl-Bn	R	c-Hex	C(O)N(Ph)	1	485
118	H	H	4-Cl-Bn	R	c-Hex	C(S)N(Et)	1	451
119	H	H	4-Cl-Bn	R	c-Hex	C(S)N(Et)(Me)	1	465
120	H	H	4-Cl-Bn	R	c-Hex	$S(O)_2Me$	1	456
121	H	H	4-Cl-Bn	R	c-Pen	$C(O)CH(Me)_2$	1	420
122	H	H	4-Cl-Bn	R	c-Hep	$C(O)CH(Me)_2$	1	448
123	H	H	4-Cl-Bn	R	ph	$C(O)CH(Me)_2$	1	428
124	H	H	4-Cl-Bn	R	2-MeO-Ph	$C(O)CH(Me)_2$	1	458
125	H	H	4-Cl-Bn	R	3-MeO-Ph	$C(O)CH(Me)_2$	1	458
126	H	H	4-Cl-Bn	R	2-Cl-Ph	$C(O)CH(Me)_2$	1	462
127	H	H	4-Cl-Bn	R	2-F-Ph	$C(O)CH(Me)_2$	1	446
128	H	H	4-Cl-Bn	R	3-F-Ph	$C(O)CH(Me)_2$	1	446
129	H	H	4-Cl-Bn	R	4-F-Ph	$C(O)CH(Me)_2$	1	446
130	H	H	4-Cl-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	1	464
131	H	H	4-Cl-Bn	R	2,4-diF-Ph	$C(O)CH(Me)_2$	1	464
132	H	H	4-Cl-Bn	R	2,5-diF-Ph	$C(O)CH(Me)_2$	1	464
133	H	H	4-Cl-Bn	R	2,6-diF-Ph	$C(O)CH(Me)_2$	1	464
134	H	H	4-Cl-Bn	R	3,4-diF-Ph	$C(O)CH(Me)_2$	1	464
135	H	H	4-Cl-Bn	R	2-F-4-MeO-Ph	$C(O)CH(Me)_2$	1	476
136	H	H	4-Cl-Bn	S	c-Hex	$C(O)CH(Me)_2$	1	434
137	H	H	4-Br-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	479
138	H	H	3,4-di-F-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	468
139	H	H	4-F-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	1	448
140	H	H	4-HO-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	416
141	H	H	4-MeO-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	1	448
142	H	H	(c-Hex)-CH_2	R	c-Hex	$C(O)CH(Me)_2$	1	406
143	N-diMe-Gly	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	519
144	(R)Ala	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	505
145	β-Ala	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	519
146	N-diMe-β-Ala	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	547
147	(S)His	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	620
148	(R)Pro	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	531

149	N-Me-(R)Pro	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	617
150	(R)Tic	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	591
151	(R)Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	517
152	(R)Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)C(Me)_3$	2	531
153	(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	2	547
154	(R)Pyd-2-CH_2	H	4-Cl-Bn	R	2,4-diF-Ph	$C(O)CH(Me)_2$	2	547
155	(S)Pyd-2-CH_2	H	4-F-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	2	547
156	(2R, 4S)-4F-Pyd-2-CH_2	H	4-Cl-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	2	554
157	(S)Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	517
158	(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2,3-diF-Ph	$C(O)CH(Me)_2$	2	547
159	(S)Pyd-2-CH_2	H	4-Cl-Bn	R	2,4-diF-Ph	$C(O)CH(Me)_2$	2	547
160	(R)-1-Me-Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	545
161	(R)-1-Me-Pid-3-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	545



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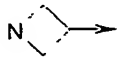
Example	R^1	R^2	R^3	*	R^4	R^5	n	MS(M+1)
162	H	H	4-Cl-Bn		c-Hex	$C(O)CH(Me)_2$	1	406
163	H	H	4-Cl-Bn	R	c-Hex	$C(O)C(Me)_3$	1	420
164	H	H	4-Cl-Bn	R	c-Hex	C(O)OMe	1	394
165	H	H	4-Cl-Bn	R	c-Hex	$C(O)N(Me)_2$	1	407
166	H	H	4-Cl-Bn	R	c-Hex	$S(O)_2Me$	1	414
167	H	H	4-Cl-Bn	R	c-Pen	$C(O)CH(Me)_2$	1	392
168	H	H	4-Cl-Bn	R	c-Hep	$C(O)CH(Me)_2$	1	420
169	H	H	4-Cl-Bn	R	i-Pr	$C(O)CH(Me)_2$	1	466
170	H	H	4-Cl-Bn	R	(c-Hex)-CH_2	$C(O)CH(Me)_2$	1	420
171	H	H	4-Cl-Bn	R	2-Me-(c-Hex)	$C(O)CH(Me)_2$	1	420
172	H	H	4-Cl-Bn	R	i-Bu	$C(O)CH(Me)_2$	1	480
173	Gly	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	463
174	N-diMe-Gly	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	505
175	(S)His	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	592
176	N-BOC-(S)His	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	692

177	(R)Pro	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	503
178	N-Me-(R)Pro	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	517
179	(S)Pro	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	503
180	(R)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	517
181	N-Me-(R)Pid-2-CO	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	531
182	(R)Tic	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	1	565
183		H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	489
184	(R)Pyd-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	589
185	(R)-1-Me-Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	631
186	(R)Pid-2-CH_2	H	4-Cl-Bn	R	c-Hex	$C(O)CH(Me)_2$	2	617

Example 187: (2R)-2-amino-N-{(3S)-3-{[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

Step A: (2R)-2-(BOC)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 1 using 3(S)-3-{cyclohexyl[(2R)-2-methyl-3-acetyloxypropionyl]amino}pyrrolidine.

MS[M+H] = 520(M+1)

Step B: (2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

To a solution of (2R)-2-(BOC)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide, prepared in Step A, in DCM (7 mL) was added TFA (7 mL). After being stirred at rt for 1 h, the reaction mixture was concentrated *in vacuo* to give the title compound. The product was used without further purification.

MS[M+1] = 420(M+1)

Step C: (2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

To a solution of (2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA, prepared in Step B, (592 mg, 1.00 mmol) in MeOH/H_2O = 1/1, 10 mL) was added

LiOH (70 mg, 2.00 mmol) portionwise. After the reaction mixture was stirred at rt for 30 min., the solvent was removed *in vacuo*, and the residue was dilute with a saturatd aqueous $NaHCO_3$ solution. The organic material was extracted with EtOAc, and the extracts were dried over $MgSO_4$ and concentrated *in vacu*. The residue was purified by HPLC to give the title compound (495 mg, 90.0%).

MS[M+1] = 420(M+1)

Step D: (2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

(2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in the above Step C was dissolved in methanol, and passed though HCl-substituted ion exchange resin to give the title compound.

MS[M+1] = 420(M+1)

Example 188: (2R)-2-(aminoacetyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

Step A: (2R)-2-[(BOC)aminoacetyl]amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 1 using (2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step B of Example 187 and N-BOC-Gly.

MS[M+H] = 635(M+1)

Step B: (2R)-2-(aminoacetyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step B of Example 187 using (2R)-2-[(BOC)aminoacetyl]amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A.

MS[M+H] = 535(M+1)

Step C: (2R)-2-(aminoacetyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step C

of Example 187 using (2R)-2-(aminoacetyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step B.

MS[M+H] = 493(M+1)

Step D: (2R)-2-(aminoacetyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-(aminoacetyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Step C.

MS[M+H] = 493(M+1)

Example 189: (2R)-2-(dimethyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

Step A: (2R)-2-(dimethyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (2R)-2-amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA ,prepared in Step B of Example 187, (592 mg, 1.00 mmol) and formaline(0.72 mL, 10.0 mmol) in DCE(3 mL) was added $NaBH(OAc)_3$(460 mg, 2.00 mmol). After the being stirred at rt for 4 h, the reaction mixture was quenched with an aqueous $NaHCO_3$ solution and extracted with DCM followed by EtOAc. The extracts were dried over $MgSO_4$ and concentrated *in vacuo*, and the residue was purified by column chomatography (eluent: DCM/MeOH = 9/1) to give the title compound (512 mg, 90.0%).

MS[M+H] = 563(M+1)

Step B: (2R)-2-(dimethyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step C of Example 187 using (2R)-2-(dimethyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-acetyloxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in the above Step A.

MS[M+H] = 521(M+1)

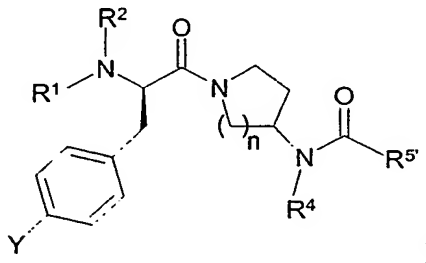
Step C: (2R)-2-(dimethyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-(dimethyl)amino-N-{(3S)-3-[cyclohexyl((2R)-2-methyl-3-hydroxypropionyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in the above Step B.

MS[M+H] = 521(M+1)

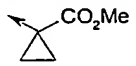
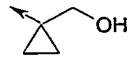
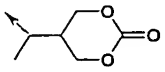
Example 190-293:

The compounds below were prepared following the procedure described in Example 187-189 using pyrrolidine and piperidine derivatives prepared in the above Intermediates.



X HCl

Exm.	R^1	R^2	Y	R^4	$R^{5'}$	*	n	x	MS [M+1]
190	H	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	464
191	H	H	Cl	c-Hex	$C(Me)_2OH$	S	1	1	436
192	H	H	Cl	c-Hex	$C(Me)_2(CH_2)_2OH$	S	1	1	478
193	H	H	Cl	c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	466
194	H	H	Cl	c-Hex	$C(Me)_2CH_2OH$	R	1	1	464
195	H	H	Cl	c-Hex	$C(Me)_2CH_2OMe$	S	1	1	464
196	H	H	Cl	c-Hex	$C(Me)_2CH_2OBn$	S	1	1	540
197	H	H	Cl	c-Hex	$C(-(CH_2)_4-)CH_2OH$	S	1	1	464
198	H	H	Cl	c-Hex	$C(Me)_2(CH_2)_3O$-(2,4-diMe-Ph)	S	1	1	582
199	H	H	Cl	c-Hex	$C(Me)CH_2OAc$	S	1	1	478
200	H	H	Cl	c-Hex	$C(-(CH_2)_2-)C(O)OH$	S	1	1	461

201	H	H	Cl	c-Hex	N(n-Pr)	S	1	2	450
202	H	H	Cl	c-Hex	N(Et)	S	1	2	436
203	H	H	Cl	c-Hex	N(n-Bu)	S	1	2	464
204	H	H	Cl	c-Hex	3-OH-Ph	S	1	1	470
205	H	H	Cl	c-Hex	4-OH-Ph	S	1	1	470
206	H	H	Cl	c-Hex	2-(CH_2OH)-1-(c-penten)-1-yl	S	1	1	474
207	H	H	Cl	c-Hex	2-(CH_2OH)-1-(c-Hexen)-1-yl	S	1	1	488
208	H	H	Cl	c-Hex	1-Nos-Pid-4-yl	S	1	1	646
209	H	H	Cl	c-Hex	Pid-4-yl	S	1	2	461
210	H	H	Cl	c-Hex	C(OH)(i-Pr)	S	1	1	449
211	H	H	Cl	c-Hex	$CH_2C(Me)_2OH$	S	1	1	449
212	H	H	Cl	c-Hex		S	1	1	475
213	H	H	Cl	c-Hex		S	1	1	447
214	H	H	H	c-Hex	$C(Me)_2CH_2OH$	S	1	1	415
215	H	H	F	c-Hex	$C(Me)_2CH_2OH$	S	1	1	433
216	H	H	Me	c-Hex	$C(Me)_2CH_2OH$	S	1	1	429
217	H	H	MeO	c-Hex	$C(Me)_2CH_2OH$	S	1	1	445
218	Me	Me	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	478
219	Me	Me	Cl	c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	494
220	Me	Me	Cl	c-Hex		S	1	1	520
221	Me	Me	H	c-Hex	$C(Me)_2CH_2OH$	S	1	1	443
222	Me	Me	F	c-Hex	$C(Me)_2CH_2OH$	S	1	1	461
223	Me	Me	Me	c-Hex	$C(Me)_2CH_2OH$	S	1	1	457
224	Me	Me	MeO	c-Hex	$C(Me)_2CH_2OH$	S	1	1	473
225	Et	Et	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	506
226	iPr	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	492
227	-(CH_2)$_5$-		Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	518
228	$HOCH_2C(Me)_2C(O)$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	0	550
229	Imidazol-2-yl	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	2	530
230	Imidazol-4-yl	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	2	530
231	(i-Pr)C(O)	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	0	520

232	Gly	H	Cl	c-Hex	$C(Me)CH_2OH$	S	1	1	507
233	NH_2-$(CH_2)_4$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	535
234	N-diMe-Gly	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	535
235	HO-$(CH_2)_3$-C(O)	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	0	536
236	EtC(O)	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	0	506
237	Pyd-3-yl	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	2	519
238	(S)Pyd-2-CH_2-	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	2	533
239	$MeOC(O)CH_2$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	0	522
240	DTic	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	609
241	NH_2-$(CH_2)_2$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	2	493
242	(Me)NH-$(CH_2)_2$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	2	507
243	Pyd-2-CH_2-	H	Cl	c-Hex	2-(CH_2OH)-1-(c-Penen)-1-yl	S	1	2	557
244	H	H	Cl	4-cis-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	464
245	H	H	Cl	4-trans-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	464
246	H	H	Cl	4-t-Bu-c-Hex	$C(Me)_2CH_2OH$	S	1	1	506
247	H	H	Cl	4-Ph-c-Hex	$C(Me)_2CH_2OH$	S	1	1	526
248	H	H	Cl	4,4-diMe-c-Hex	$C(Me)_2CH_2OH$	S	1	1	478
249	H	H	Cl	Pid-4-yl	$C(Me)_2CH_2OH$	S	1	2	451
250	H	H	Cl	4-oxo-c-Hex	$C(Me)_2CH_2OH$	S	1	1	464
251	H	H	Cl	4,4-diF-c-Hex	$C(Me)_2CH_2OH$	S	1	1	486
252	H	H	Cl	4-OH-c-Hex	$C(Me)_2CH_2OH$	S	1	1	466
253	H	H	Cl	4-F-c-Hex	$C(Me)_2CH_2OH$	S	1	1	468
254	H	H	Cl	Spiro[2,5]octane	$C(Me)_2CH_2OH$	S	1	1	476
255	H	H	Cl	4-cis-Et-c-Hex	$C(Me)_2CH_2OH$	S	1	1	478
256	H	H	Cl	4-trans-Et-c-Hex	$C(Me)_2CH_2OH$	S	1	1	478
257	H	H	Cl	4-cis-Me-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	480
258	H	H	Cl	4-trans-Me-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	480
259	H	H	Cl	4,4-diMe-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	494
270	Me	Me	Cl	4-cis-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	492
271	Me	Me	Cl	4-trans-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	492
272	Me	Me	Cl	4-t-Bu-c-Hex	$C(Me)_2CH_2OH$	S	1	1	534
273	Me	Me	Cl	4,4-diMe-c-Hex	$C(Me)_2CH_2OH$	S	1	1	514
274	Me	Me	Cl	4-cis-Et-c-Hex	$C(Me)_2CH_2OH$	S	1	1	506
275	Me	Me	Cl	4-trans-Et-c-Hex	$C(Me)_2CH_2OH$	S	1	1	506
276	Me	Me	Cl	4-cis-Me-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	508

277	Me	Me	Cl	4-trans-Me-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	508
278	Me	Me	Cl	4,4-diMe-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	522
279	H	H	Cl	2,3-diF-Ph	$C(Me)_2CH_2OH$	S	1	1	480
280	H	H	Cl	3,5-DiMe-Ph	$C(Me)_2CH_2OH$	R,S	1	1	472
281	H	H	Cl	2,5-diF-Ph	$C(Me)_2CH_2OH$	R,S	1	1	480
282	H	H	Cl	4-Me-Ph	$C(Me)_2CH_2OH$	R,S	1	1	458
283	H	H	Cl	Ph	$C(Me)_2CH_2OH$	R,S	1	1	444
284	H	H	Cl	2-Adamantyl	$C(Me)_2CH_2OH$	S	1	1	472
285	H	H	Cl	c-Hex	$C(Me)_2CH_2OH$	R	2	1	464
286	H	H	Cl	c-Hex	$C(Me)(CH_2OH)_2$	R	2	1	479
287	H	H	Cl	c-Hex	2-(CH_2OH)-1-(c-penten)-1-yl	S	2	1	488
288	H	H	Cl	c-Hex	2-(CH_2OH)-1-(c-hexen)-1-yl	S	2	1	502
289	H	H	Cl	4-cis-Me-c-Hex	$C(Me)_2CH_2OH$	S	2	2	477
290	H	H	Cl	4,4-diMe-c-Hex	$C(Me)_2CH_2OH$	S	2	2	591
291	H	H	Cl	4-trans-Me-c-Hex	$C(Me)_2CH_2OH$	S	2	2	493
292	(R)Pyd-2-CH_2-	H	Cl	2,3-diF-Ph	$C(Me)_2CH_2OH$	S	2	2	576
293	(R)Pyd-2-CH_2-	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	2	2	546

Example 294: (2R)-2-[isopropyl(methyl)]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

Step A: (2R)-2-[isopropyl(methyl)]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step A of Example 189 using (2R)-2-(isopropyl)amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Example 226 (purified by HPLC).

MS[M+H] = 492(M+1)

Step B: (2R)-2-[isopropyl(methyl)]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-[isopropyl(methyl)]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Step A.

MS[M+H] = 492(M+1)

Example 295: (2R)-2-[(2-hydroxy-2-oxo)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

Step A: (2R)-2-[(2-hydroxy-2-oxo)ethyl]amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

To a solution of (2R)-2-amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide, prepared in Example 190, (492 mg, 1.00 mmol) in acetonitrile (5 mL) were added DIEA (0.435 mL, 2.50 mmol) was added dropwise and methylbromoacetate (0.085 mL, 1.00 mmol). After the reaction mixture was stirred at 60℃ for 4 h, the solvent was removed *in vacuo*, and the residue was diluted with an aqueous $NaHCO_3$ solution. The organic material was extracted with EtOAc, and the extracts were washed with 1N HCl, dried over $MgSO_4$, and concentrated *in vacuo* to give the title compound. The product was used without further purification.

MS[M+H] = 564(M+1)

Step B: (2R)-2-[(2-hydroxy-2-oxo)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step C of Example 187 using (2R)-2-[(2-hydroxy-2-oxo)ethyl]amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Step A.

MS[M+H] = 508(M+1)

Step C: (2R)-2-[(2-hydroxy-2-oxo)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-[(2-hydroxy-2-oxo)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Step B.

MS[M+H] = 508(M+1)

Example 296: (2R)-2-[di(hydroxyacetyl)]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

The title compound was prepared following the procedure described in Example 295 using (2R)-2-amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide.

MS[M+H] = 566(M+1)

Example 297: (2R)-2-amino-N-{(3S)-3-[cyclohexyl(4-aminobutylcarbamoyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

Step A: (2R)-2-amino-N-{(3S)-3-[cyclohexyl(4-aminobutylcarbamoyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Step B of Example 187 using (3S)-3-[cyclohexyl[4-(BOC)aminobutylcarbamoyl]amino]pyrrolidine prepared in Intermediate 159.

MS[M+H] = 549(M+1)

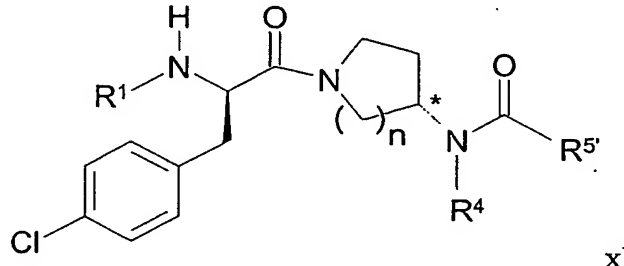
Step B: (2R)-2-amino-N-{(3S)-3-[cyclohexyl(4-aminobutylcarbamoyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-amino-N-{(3S)-3-[cyclohexyl(4-aminobutylcarbamoyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA prepared in Step A.

MS[M+H] = 549(M+1)

Example 298-357:

The compounds below were prepared following the procedure described in Example 189 and 297 using pyrrolidine and piperidine derivatives prepared in the above Intermediates.



xHCl

Exm.	R^1	R^4	$R^{5'}$	*	n	x	MS [M+1]
298	H	c-Hex	N-$(CH_2)_3$-NH_2	S	1	2	450
299	H	c-Hex	N-$(CH_2)_2$-NH_2	S	1	2	436
300	H	c-Hex	N-$(CH_2)_2$-OH	S	1	1	437
301	H	c-Hex	N-$(CH_2)_2$-OMe	S	1	1	451
302	H	c-Hex	(3S)-3-(OH)-Pyd-1-yl	S	1	1	463
303	H	c-Hex	(2S)-2-($HOCH_2$)-Pyd-1-yl	S	1	1	477
304	H	c-Hex	N$[(CH_2)_2OH]_2$	S	1	1	495
305	H	c-Hex	N$[(CH_2)_3OH]_2$	S	1	1	523
306	H	c-Hex	N(Me)$(CH_2)_2$OH		2	1	465
307	H	c-Hex	N(Et)$(CH_2)_2$OH		2	1	479
308	H	c-Hex	N(Et)$(CH_2)_3$OH		2	1	493
309	H	c-Hex	N(Et)$(CH_2)_2$F		2	1	481
310	H	c-Hex	N(Et)$(CH_2)_3$F		2	1	495
311	H	c-Hex	N(n-Pr)$(CH_2)_2$OH		2	1	493
312	H	c-Hex	N(c-Pr)$(CH_2)_2$OH		2	1	491
313	H	c-Hex	N(i-Pr)$(CH_2)_2$OH		2	1	493
314	H	c-Hex	N$[(CH_2)_2OMe](CH_2)_2$OH		2	1	509
315	H	c-Hex	N$[(CH_2)_2F](CH_2)_2$OH		2	1	497
316	H	c-Hex	N(Me)$(CH_2)_2$OMe		2	1	479
317	H	c-Hex	N(H)$(CH_2)_2$OMe		2	1	465

318	H	c-Hex	N(Et)$(CH_2)_2$OMe		2	1	493
319	H	c-Hex	N[$(CH_2)_2$OMe]$_2$		2	1	523
320	H	c-Hex	N(c-Pen)[$(CH_2)_2$OMe]		2	1	533
321	H	c-Hex	N(Et)$_2$		2	1	463
322	H	c-Hex	N(Me)OMe		2	1	451
323	H	c-Hex	N(Me)[C(O)$(Me)_2CH_2$OH]		2	1	493
324	H	c-Hex	N[$(CH_2)_2$OMe][$(CH_2)_2$F]		2	1	511
325	H	c-Hex	(3S)-3-(OH)-Pyd-1-yl		2	1	477
326	H	c-Hex	(3R)-3-(OH)-Pyd-1-yl		2	1	477
327	H	c-Hex	(2R)-2-($HOCH_2$)-Pyd-1-yl		2	1	491
328	H	c-Hex	(2S)-2-($HOCH_2$)-Pyd-1-yl		2	1	491
329	H	c-Hex	(3R)-3-amino-Pyd-1-yl		2	1	476
330	H	c-Hex	(3S)-3-amino-Pyd-1-yl		2	1	476
331	H	c-Hex	(3R)-3-(OH)-Pid-1-yl		2	1	491
332	H	c-Hex	(3S)-3-(OH)-Pid-1-yl		2	1	491
333	H	c-Hex	4-(OH)-Pid-1-yl		2	1	491
334	H	c-Hex	4-amino-Pid-1-yl		2	1	490
335	(R)Pyd-2-CH_2	c-Hex	N(n-Pr)$(CH_2)_2$OH		2	2	576
336	(R)Pyd-2-CH_2	c-Hex	N[$(CH_2)_2$OH]$_2$		2	2	578
337	(R)Pyd-2-CH_2	c-Hex	N(Me)OMe		2	2	534
338	(R)Pyd-2-CH_2	c-Hex	N(Me)[$C(Me)_2CH_2$OH]		2	2	562
339	(R)Pyd-2-CH_2	c-Hex	N(Et)$(CH_2)_2$OH		2	2	576
340	(R)Pyd-2-CH_2	c-Hex	N[$(CH_2)_2$OMe]$_2$		2	2	620
341	(R)Pyd-2-CH_2	c-Hex	N(c-Pr)$(CH_2)_2$OH		2	2	588
342	(R)Pyd-2-CH_2	c-Hex	(3S)-3-(OH)-Pyd-1-yl		2	2	560
343	(R)Pyd-2-CH_2	c-Hex	(2R)-2-($HOCH_2$)-Pyd-1-yl		2	2	574
344	(R)Pyd-2-CH_2	c-Hex	4-(OH)-Pid-1-yl		2	2	574
345	(R)Pyd-2-CH_2	c-Hex	(3R)-3-(OH)-Pid-1-yl		2	2	574
346	(S)Pyd-3-yl	c-Hex	N[Et]$_2$		2	2	532
347	(S)Pyd-3-yl	c-Hex	N(Me)$(CH_2)_2$OH		2	2	548
348	NH_2-$(CH_2)_2$-	c-Hex	N[$(CH_2)_2$OH]$_2$		2	2	552
349	(Me)NH-$(CH_2)_2$	c-Hex	N[$(CH_2)_2$OH]$_2$		2	2	566
350	(i-Pr)NH-$(CH_2)_2$-	c-Hex	N(Et)$(CH_2)_2$OH		2	2	564
351	Mor-$(CH_2)_2$	c-Hex	N(c-Pr)$(CH_2)_2$OH		2	2	604
352	Mor-$(CH_2)_2$	c-Hex	N(Et)$(CH_2)_2$OH		2	2	592

353	Mor-$(CH_2)_2$	c-Hex	$N[(CH_2)_2OMe]_2$		2	2	636
354	H	2,3-diF-Ph	$N(Me)(CH_2)_2OH$		2	1	495
355	H	2,3-diF-Ph	$N(Me)(CH_2)_2OMe$		2	1	495
356	(R)Pyd-2-CH_2	2,3-diF-Ph	$N(Me)(CH_2)_2OH$		2	2	578
357	(R)Pyd-2-CH_2	2,3-diF-Ph	$N(Me)(CH_2)_2OMe$		2	2	592

Example 358: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-[(2-nitrobenzene)sulfonyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA ,prepared in Example 1 (420 mg, 1 mmol), in DM F(10 mL) were added TEA (280 $\mu\ell$, 2 mmol) and (2-nitrobenzene)sulfonylchloride (222 mg, 1.00 mmol). After the being stirred at rt for 4 h, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution and was extracted with DCM followed by EtOAc. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chomatography (eluent: EtOAc/Hex = 1/3) to give the title compound (568 mg, 94.0%).

MS[M+H] = 585(M+1)

Step B: (2R)-2-{(2-nitrobenzene)sulfonyl[2-(dimethylamino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (2R)-2-[(2-nitrobenzene)sulfonyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide(200 mg, 0.331 mmol), prepared in Step A, in DMF (3 mL) were added K_2CO_3 and 2-(dimethylamino)ethyl chloride (HCl salts, 73.9 mg, 0.533 mmol). After being stirred at rt for 24 h, the reaction mixture was concentrated *in vacuo,* and the residue was diluted a saturated aqueous NH_4Cl solution. The organic material was extracted with EtOAc, and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: EtOAc/Hex = 1/1) to give the title compound (205 mg, 92.0%).

MS[M+H] = 585(M+1)

Step C: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

To a solution of (2R)-2-{(2-nitrobenzene)sulfonyl[2-(dimethylamino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide (100 mg, 0.148 mmol), prepared in Step B, in DMF (3 mL) were added K_2CO_3 (61.3 mg, 0.429 mmol) and thiobenzene (45.6 $\mu\ell$, 0.429 mmol). After being stirred at rt for 2 h, the reaction mixture was concentrated *in vacuo* to remove DMF, and the residue was diluted with water. The organic material was extracted with EtOAc, and the extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by HPLC to give the title compound (89 mg, 84.0%).

MS[M+H] = 470(M+1)

Example 359: (2R)-2-[2-(methylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-{(2-nitrobenzene)sulfonyl[2-(BOC)aminoethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step B of Example 358 using (2R)-2-[(2-nitrobenzene)sulfonyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A of Example 358 and N-BOC-aminoethylbromide.

MS[M+H] = 642(M+1)

Step B: ((2R)-2-{(2-nitroenzene)sulfonyl[2-(methyl(BOC)amino)ethyl]}amino-N-{(3S)-3-[(cyclohexyl(isobutyryl)amino)pyrrolidine-1-yl]-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 128 using (2R)-2-{(2-nitrobenzene)sulfonyl[2-(BOC)aminoethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in the above Step A and methyliodide.

MS[M+H] = 657(M+1)

Step C: (2R)-2-{2-[methyl(BOC)amino]ethyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step C

of Example 358 using (2R)-2-{[2-BOC(methyl)amino]ethyl(2-nitrobenzenesulfonyl)}amino-N-{(3S)-3-[(cyclohexyl(isobutyryl)amino)pyrrolidine-1-yl]-3-(4-chlorophenyl)propionamide prepared in Step B.

MS[M+H] = 657(M+1)

Step D: (2R)-2-[2-(methylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA 염

The title compound was prepared following the procedure described in Step B of Example 1 using (2R)-2-{2-[methyl(BOC)amino]ethyl}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step C.

MS[M+H] = 657(M+1)

Example 360: (2R)-2-(2-aminoethyl)amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-[2-(BOC)aminoethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step C of Example 358 using (2R)-2-{(2-nitrobenzene)sulfonyl[2-(BOC)aminoethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A of Example 359.

MS[M+H] = 563(M+1)

Step B: (2R)-2-(2-aminoethyl)amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Step B of Example 1 using (2R)-2-[2-(BOC)aminoethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A.

MS[M+H] = 463(M+1)

Example 361: (2R)-2-[2-(acetylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Example 358 using acetylaminoethyl bromide.

MS[M+H] = 505(M+1)

Example 362: (2R)-2-{methyl[2-(methylamino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-{methyl[2-(BOC)aminoethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 3 using (2R)-2-[2-(BOC)aminoethyl]amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A of Example 360 and formaline.

MS[M+H] = 577(M+1)

Step B: (2R)-2-{methyl[2-(methyl(BOC)amino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 128 using (2R)-2-{methyl[2-(BOC)aminoethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in the above Step A and methyliodide.

MS[M+H] = 591(M+1)

Step C: (2R)-2-{methyl[2-(methylamino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Step B of Example 1 using (2R)-2-{methyl[2-[methyl(BOC)amino]ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step B.

MS[M+H] = 491(M+1)

Example 363: (2R)-2-{methyl[2-(amino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

2TFA

The title compound was prepared following the procedure described in Step B of Example 1 using (2R)-2-{methyl[2-(BOC)aminoethyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A of Example 362.

MS[M+H] = 477(M+1)

Example 364: (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

Step A: (2R)-2-{methyl[(2-nitrobenzene)sulfonyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step B of Example 358 using (2R)-2-[(2-nitrobenzene)sulfonyl]amino-N-{(3S)-3-[cyclohexyl(isopropyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A of Example 358 and methyliodide.

MS[M+H] = 619(M+1)

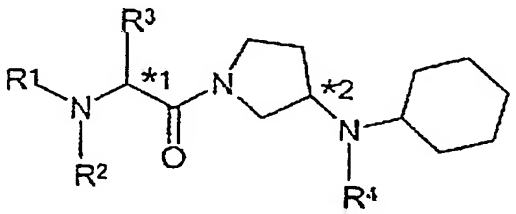
Step B: (2R)-(methyl)amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step Cof Example 358 using (2R)-2-{methyl[(2-nitrobenzene)sulfonyl]}amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step A.

MS[M+H] = 434(M+1)

Example 365-388:

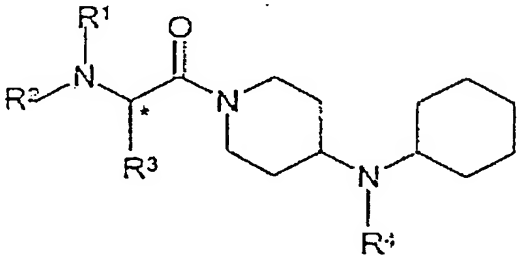
The compounds below were prepared following the procedure described in Example 358 and 364 using piperidine derivatives prepared in the above Intermediates.



nTFA

Example	R^1	R^2	R^3	*1	*2	R^4	n	MS

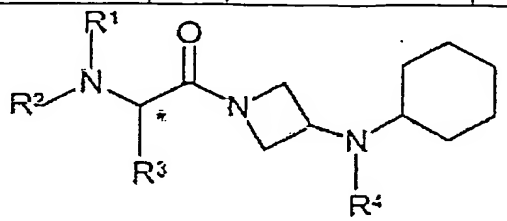
								(M+1)
365	MeO_2C-CH_2	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	492
366	N-Me-Gly	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	1	491
367	N-Me-β-Ala	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	1	505
368	(Me)NH-$(CH_2)_2$	H	4-Cl-Bn	R	R	C(O)CH(Me)$_2$	2	477
369	$(Me)_2N$-$(CH_2)_2$	H	4-Cl-Bn	R	S	C(O)C(Me)$_3$	2	505
370	$(Me)_2N$-$(CH_2)_2$	H	Bn	R	S	C(O)CH(Me)$_2$	2	457
371	$(Me)_2N$-$(CH_2)_2$	H	(c-Hex)-CH_2-	R	S	C(O)CH(Me)$_2$	2	463
372	$(Me)_2N$-$(CH_2)_2$	Me	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	484
373	$(Et)_2N$-$(CH_2)_2$	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	519
374	[Me(Et)]N-$(CH_2)_2$	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	505
375	(aziridine-1-yl)-$(CH_2)_2$	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	489
376	(3R)Pyd-3-yl	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	489
377	(azetidine-2-yl)-CO	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	503
378	Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	S	C(O)CH(Me)$_2$	2	517



nTFA

Example	R^1	R^2	R^3	*	R^4	n	MS(M+1)
379	Me	H	4-Cl-Bn	R	C(O)CH(Me)$_2$	1	448
380	MeO_2C-CH_2	H	4-Cl-Bn	R	C(O)CH(Me)$_2$	1	506
381	NH_2-$(CH_2)_2$	H	4-Cl-Bn	R	C(O)CH(Me)$_2$	2	477

382	$(Me)_2N-(CH_2)_2$	H	4-Cl-Bn	R	$C(O)CH(Me)_2$	2	505
383	(3R)Pyd-3-yl	H	4-Cl-Bn	R	$C(O)CH(Me)_2$	2	503
384	(3R)Pyd-3-yl	H	Bn	R	$C(O)CH(Me)_2$	2	489



nTFA

Example	R^1	R^2	R^3	*	R^4	n	MS(M+1)
385	MeO_2C-CH_2	H	4-Cl-Bn	R	$C(O)CH(Me)_2$	1	478
386	$(Me)_2N-(CH_2)_2$	H	4-Cl-Bn	R	$C(O)CH(Me)_2$	2	505
387	$(Me)_2N-(CH_2)_2$	H	4-Cl-Bn	R	$C(O)C(Me)_3$	2	519
388	Pyd-1-$(CH_2)_2$	H	4-Cl-Bn	R	$C(O)CH(Me)_2$	2	503

Example 389: (2R)-2-[(dimethylamino)methylene]amino-N-{(3S)-3-{[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

(2R)-2-amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA (51. 4 mg, 0.1 mmol) and dimethylformamide dimethoxyformat (0.24 mg, 0.2 mmol) were dissolved in methanol (5 mL). After the reaction mixture was stirred at rt for 1 h, the solvent was distilled out in vacuo to remove, the residue was purified by HPLC to give the title compound (46 mg, 99%).

MS[M+H] = 477 (M+1)

Example 390: (2R)-2-(carboxymethyl)amino-N-{(3S)-3-{[cyclohexyl(isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step B of Example 135 using Example 365.

MS[M+H] = 478 (M+1)

Example 391: (2R)-2-(carboxymethyl)amino-N-{4-[cyclohexyl(isobutyryl)amino]piperidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step B of Example 135 using Example 380.

MS[M+H] = 492 (M+1)

Example 392: (2R)-2-(carboxymethyl)amino-N-{(3S)-3-[cyclohexyl(isobutyryl)amino]azetidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

The title compound was prepared following the procedure described in Step B of Example 135 using Example 385.

MS[M+H] = 464 (M+1)

Example 393: (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

Step A: (2R)-2-[(2-nitrobenzene)sulfonyl]amino-3-(4-chlorophenyl)propionic acid methylester

The title compound was prepared following the procedure described in Step C of Example 151 using p-chlorophenylalanine methylester.

MS[M+H] = 399(M+1)

Step B: (2R)-2-{[(2-nitrobenzene)sulfonyl]methyl}amino-3-(4-chlorophenyl)propionic acid methylester

To a solution of (2R)-2-[(2-nitrobenzene)sulfonyl]amino-3-(4-chlorophenyl)propionic acid methylester(1 g, 2.51 mmol), prepared in Step A, in DMF (10 mL)were added K_2CO_3 (678 mg, 5.00 mmol) and methyliodide (427 mg, 3.01 mmol). After the reaction solution was stirred at rt for 12 h, the solvent was concentrated *in vacuo*, and the residue was diluted with aqueous 1n HCl solution. The organic material was extracted with EtOAc, and the extracts were washed with 1N HCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (eluent: EtOAc:Hex = 1/2) to give the title compound (932 mg, 90.0%).

MS[M+H] = 413(M+1)

Step C: (2R)-2-{[(2-nitrobenzene)sulfonyl]methyl}amino-3-(4-chlorophenyl)propionic acid

The title compound was prepared following the procedure described in Step C of Example 187 using (2R)-2-{[(2-nitrobenzene)sulfonyl]methyl}amino-3-(4-chlorophenyl)propionic acid methyl ester prepared in Step B.

MS[M+H] = 399(M+1)

Step D: (2R)-2-{[(2-nitrobenzene)sulfonyl]methyl}amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 188 using (2R)-2-{[(2-nitrobenzene)sulfonyl]methyl}amino-3-(4-chlorophenyl)propionic acid prepared in Step B and (3S)-3-N-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine prepared in Intermediate 81.

MS[M+H] = 521(M+1)

Step E: (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

To a solution of (2R)-2-{[(2-nitrobenzene)sulfonyl]methyl}amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide, prepared in Step D, (691 mg, 1.00 mmol) in DMF (5 mL) were added K_2CO_3 (270 mg, 2.00 mmol) and mercaptobenzene (0.154 mL, 1.5 mmol), and the mixture was stirred at rt for 2 h. The reaction mixture was concentrated *in vacuo* and the residue was diluted with aqueous 1N HCl solution. The organic material was extracted with EtOAc, and the extracts were washed with 1N HCl, dried over $MgSO_4$, and concentrated *in vacuo* to give the title compound. This product was used without further purification.

MS[M+H] = 506(M+1)

Step F: (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Step C of Example 187 using (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Step E.

MS[M+H] = 464(M+1)

Step G: (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

The title compound was prepared following the procedure described in Step D

of Example 187 using (2R)-2-(methyl)amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA prepared in Step F.

MS[M+H] = 464(M+1)

Example 394: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

Step A: (2R)-2-[(2-nitrobenzene)sulfonyl]amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step A of Example 358 using (2R)-2-amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino] pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide prepared in Example 190 and 2-nitrobenzenesulfonylchloride.

MS[M+H] = 677(M+1)

Step B: (2R)-2-{(2-nitrobenzene)sulfonyl[2-(dimethylamino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl) propionamide.

The title compound was prepared following the procedure described in Step B of Example 358 using (2R)-2-[(2-nitrobenzene)sulfonyl]amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl) propionamide prepared in Step A and dimethylaminoethylchloride.

MS[M+H] = 748(M+1)

Step C: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide

The title compound was prepared following the procedure described in Step C of Example 358 using (2R)-2-{(2-nitrobenzene)sulfonyl[2-(dimethylamino)ethyl]}amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl) propionamide prepared in Step B.

MS[M+H] = 565(M+1)

Step D: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

The title compound was prepared following the procedure described in Step B of Example 187 using (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(acetyloxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl) propionamide prepared in Step C.

MS[M+H] = 521(M+1)

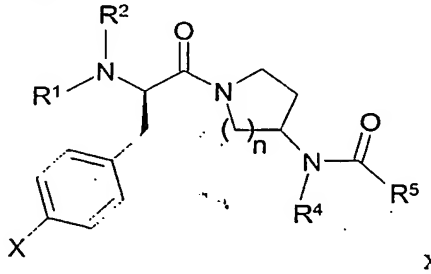
Step E: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-[2-(dimethylamin)oethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA prepared in Step D.

MS[M+H] = 521(M+1)

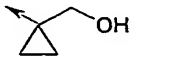
Example 395-463:

The compounds below were prepared following the procedure described in Example 394 using pyrrolidine or piperidine derivatives prepared in the above Intermediates.



xHCl

Exm.	R^1	R_2	X	R^4	$R^{5'}$	*	n	x	MS[M+1]
395	Me	H	Cl	c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	480
396	Me	H	Cl	c-Hex	$C(Me)_2CH_2OMe$	S	1	1	478
397	Me	H	Cl	c-Hex	$C(Me)_2CH_2OMOM$	S	1	1	508

398	Me	H	Cl	c-Hex		S	1	1	462
399	Me	H	Cl	4-cis-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	478
400	Me	H	Cl	4-trans-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	478
401	Me	H	Cl	4-diMe-c-Hex	$C(Me)_2CH_2OH$	S	1	1	492
402	Me	H	Cl	4-t-Bu-c-Hex	$C(Me)_2CH_2OH$	S	1	1	520
403	Me	H	Cl	4,4-diF-c-Hex	$C(Me)_2CH_2OH$	S	1	1	500
404	Me	H	Cl	Spiro[2.5]octane	$C(Me)_2CH_2OH$	S	1	1	490
405	Me	H	Cl	4-F-c-Hex	$C(Me)_2CH_2OH$	S	1	1	482
406	Me	H	Cl	4-cis-Et-c-Hex	$C(Me)_2CH_2OH$	S	1	1	492
407	Me	H	Cl	4-trans-Et-c-Hex	$C(Me)_2CH_2OH$	S	1	1	492
408	Me	H	Cl	4-cis-Me-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	494
409	Me	H	Cl	4-trans-Me-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	494
410	Me	H	Cl	4-diMe-c-Hex	$C(Me)(CH_2OH)_2$	S	1	1	508
411	Me	H	H	c-Hex	$C(Me)_2CH_2OH$	S	1	1	430
412	Me	H	F	c-Hex	$C(Me)_2CH_2OH$	S	1	1	448
413	Me	H	Me	c-Hex	$C(Me)_2CH_2OH$	S	1	1	444
414	Me	H	OMe	c-Hex	$C(Me)_2CH_2OH$	S	1	1	460
415	i-Pr	H	Cl	4-cis-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	1	506
416	i-Pr	H	Cl	4,4-diMe-c-Hex	$C(Me)_2CH_2OH$	S	1	1	520
417	i-Pr	H	Cl	4,4-diF-c-Hex	$C(Me)_2CH_2OH$	S	1	1	528
418	$-(CH_2)_4-$		Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	520
419	$-(CH_2)_5-$		Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	534
420	i-Pen	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	520
421	$MeO-(CH_2)_2-$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	508
422	$HO-(CH_2)_2-$	H	Cl	c-Hex	$C(Me)_2CH_2OH$	S	1	1	494
423	$(Me)_2N-(CH_2)_2-$	H	Cl	4-cis-Me-c-Hex	$C(Me)_2CH_2OH$	S	1	2	535
424	$(Me)_2N-(CH_2)_2-$	H	Cl	4,4-diMe-c-Hex	$C(Me)_2CH_2OH$	S	1	2	549

425	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)(CH_2OH)_2$	S	1	2	537
426	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2N(Me)_2$	S	1	3	548
427	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OMe$	S	1	2	535
428	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OMOM$	S	1	2	565
429	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OBn$	S	1	2	611
430	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2O(i\text{-}Bu)$	S	1	2	577
431	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OPh$	S	1	2	597
432	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2SPh$	S	1	2	613
433	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OCOPh$	S	1	2	625
434	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OCO(c\text{-}Hex)$	S	1	2	631
435	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OCOBn$	S	1	2	639
436	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OCOBu$	S	1	2	605
437	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OCO(i\text{-}Pr)$	S	1	2	591
438	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2CH_2OCO(2,5\text{-}diF\text{-}Ph)$	S	1	2	661
439	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$C(Me)_2OAc$	S	1	2	563
440	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$2\text{-}(HOCH_2)\text{-}1\text{-}(c\text{-}penten)\text{-}1\text{-}yl$	S	1	2	545
441	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	(3S)-3-(OH)-Pyd-1-yl	S	1	2	534
442	$(Me)_2N$-$(CH_2)_2$-	H	Cl	2,3-diF-Ph	$C(Me)_2CH_2OH$	S	1	2	566
443	$(Me)_2N$-$(CH_2)_2$-	H	Cl	2,3-diF-Ph	$N(Me)_2$	S	1	2	580
444	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(Me)OMe		2	2	522
445	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$N(Et)(CH_2)_2F$		2	2	552
446	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$N(Et)(CH_2)_3F$		2	2	566
447	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$N(Et)(CH_2)_3OH$		2	2	564
448	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	$N(Et)(CH_2)_2OH$		2	2	550

449	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(n-Pr)$(CH_2)_2$OH		2	2	564
450	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(i-Pr)$(CH_2)_2$OH		2	2	564
451	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N$[(CH_2)_2OH]_2$		2	2	566
452	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N$[(CH_2)_2OMe]_2$		2	2	594
453	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	(2R)-2-$(HOCH_2)$-Pyd-1-yl		2	2	562
454	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	4-amino-Pid-1-yl		2	2	561
455	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(Me)$(CH_2)_2$OH		2	2	536
456	$(Me)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(Me)$(CH_2)_2$OMe		2	2	550
457	$(Et)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(i-Pr)$(CH_2)_2$OH		2	2	592
458	$(Et)_2N$-$(CH_2)_2$-	H	Cl	c-Hex	N(Et)$(CH_2)_2$OH		2	2	578
459	1-pyd-$(CH_2)_2$-	H	Cl	c-Hex	N(Et)$(CH_2)_2$F		2	2	578
460	1-pyd-$(CH_2)_2$-	H	Cl	c-Hex	N(Et)$(CH_2)_3$F		2	2	592
461	(R)-3-OBn-1-Pyd-$(CH_2)_2$-	H	Cl	c-Hex	N(Et)$(CH_2)_3$F		2	1	698
462	(R)-3-OBn-1-Pyd-$(CH_2)_2$-	H	Cl	c-Hex	N(Et)$(CH_2)_2$OH		2	1	682
463	[Me(i-Pr)]N-$(CH_2)_2$-	H	Cl	c-Hex	N(Et)$(CH_2)_3$F		2	2	594

Example 464: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((2-formyl)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

Step A: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((2-formyl)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA

To a solution of (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl(hydroxypivaloyl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl, prepared in Example 394, (521 mg, 1 mmol) in DCM (5 mL) was added Dess-Martin reagent (4M in THF, 0.5 mL). After the reaction mixture was stirred at rt for 12 h, an aqueous $Na_2S_2O_3$ solution was added portionwise, and the aqueous $NaHCO_3$ solution was added when the reaction solution is clear. The organic layer was extracted with EtOAc, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by prep HPLC to give the title compound (610 mg, 85.1%).

MS[M+H] = 519(M+1)

Step B: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((2-

formyl)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((2-formyl)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2TFA prepared in Step A.

MS[M+H] = 519(M+1)

Example 465: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((methoxyimino)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

Step A: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((1-methoxyimino)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA

To a solution of (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((2-formyl)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide 2HCl, prepared in Example 464, (704 mg, 1.00 mmol) in pyridine (5 mL) was methoxyamine (HCl salts, 167 mg, 2.00 mmol). After the reaction mixture was stirred at rt for 12 h, the solvent was removed *in vacuo*, and the residue was diluted with a saturated aqueous $NaHCO_3$ solution. The organic material was extracted with EtOAc, and the extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by prep HPLC to give the title compound (500 mg, 91.2%).

MS[M+H] = 617(M+1)

Step B: (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((1-methoxyimino)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide HCl

The title compound was prepared following the procedure described in Step D of Example 187 using (2R)-2-[2-(dimethylamino)ethyl]amino-N-{(3S)-3-[cyclohexyl((1-methoxyimino)isobutyryl)amino]pyrrolidine-1-yl}-3-(4-chlorophenyl)propionamide TFA prepared in Step A.

MS[M+H] = 617(M+1)

Biological Assays

A. Binding Assay

The membrane fraction binding assay was used to identify competitive

inhibitors of ^{125}I - NDP- - MSH binding to cloned human MCRs expressed in HEK cells.

Cell lines expressing human melanocortin receptor 4 (MC4R) were grown in Φ150 mm culture dishes in DMEM (GIBCO-BRL) supplemented with 10% FBS, 200 ug/ml Geneticin (GIBCO-BRL), and antibiotics (penicillin and streptomycin) (GIBCO-BRL) in an atmosphere of 6% CO_2 at 37 °C. When the cells were fully grown, the cells were washed once with 10 ml of Ca^{++}, Mg^{++} free DPBS. The cells were incubated with 8 ml of Ca^{++}, Mg^{++} free DPBS for 15 – 30 min at 37 °C until the cells were easily detached by triturating with pipette. The cells were harvested into 50 ml of conical tubes, and spun at 1500 rpm for 5 min. The supernatant was discarded, and the cells were resuspended in 8 ml of Ca^{++}, Mg^{++} free DPBS, and spun at 1500 rpm for 5 min. The supernatant was discarded, and pellets were resuspended in 3 ml of membrane preparation buffer (50 mM Tris, pH 7.2~7.4, 4 ug/ml Leupeptin ; 10 uM Phosphoramidon ; 40 ug/ml Bacitracin ; 5 ug/ml Aprotinin ; 10 mM Pefabloc). The pellets were homogenized with dounce homogenizer (Bellco with type "B" glass pestle) using 10 – 12 strokes. The homogenate was centrifuged (Beckman XL-100K Ultracentrifuge, Rotor 45 Ti, 50 ml centrifuge tube) at 40,000 rpm (100,000 X g) for 30 min at 4 °C. The pellets were resuspended in 20 ml of membrane preparation buffer, and protein was determined by BCA assay kit (PIERCE). Aliquots were placed in tubes and stored at - 80 °C.

Membrane fraction was diluted with membrane binding buffer to make final 600 ug/ml, and 50 ul of membrane fraction containing 30 ug of membrane protein was added onto each well of 96-well assay plate. 25 ul of test compounds or 20 uM unlabelled NDP- -MSH (to make the final concentration at 5 uM) diluted with membrane binding buffer was added onto each well of 96-well assay plate. 25 ul of 0.4 nM ^{125}I - NDP- -MSH [NEN, Cat. # NEX352 (50 uCi), $t_{1/2}$ = 60 days] diluted with membrane binding buffer was added onto each well to make the final concentration of 0.1 nM. The resulting mixture was incubated for 2 h at rt. The reaction mixture was filtered with 96 well GF/C filter plate (Unifilter GF/C™, Packard) presoaked with 0.1% polyethleneimine for 30 min. The filter plate was washed 3 times with 200 ul of washing buffer (50 mM Tris pH 7.2; 20 mM NaCl) under vacuo at 8 "Hg. The filter was dried for 15 min at rt, and the bottom was sealed. 40 ul of Packard Microscint™-20 was added to each well. The top was sealed, and the radioactivity was quantitated in a Packard Topcount Microplate Scintillation Counter. The IC_{50} was defined as the concentration of test compound that results in the half

maximal inhibition of ^{125}I - NDP- - MSH binding to cloned human MCRs. The IC_{50} values obtained in the competition assay were converted to affinity constants (Ki values).

B. Functional Assay

1. Luciferase Assay.

Cell lines expressing human melanocortin receptor 4 (MC4R) were dissociated from tissue culture dishes by rinsing with Ca^{++}, Mg^{++} free DPBS, treated with 1 X Trypsin / EDTA solution for 1 min at 37 °C, and resuspended with DMEM (GIBCO-BRL) supplemented with 10% FBS. The cells were counted and diluted with DMEM supplemented with 10% FBS and 200 ug/ml of Geneticin to 5 X 10^5 cells/ ml. 90 ul of cell suspension was plated onto each well of 96-well black and clear bottom culture plates (Costar). After the incubation for 24 h in the atmosphere of 6% CO_2 at 37 °C, 10ul of NDP- -MSH and test compounds diluted in DMSO were added to each well. The final DMSO concentration was 1%. After 4 h of incubation in the atmosphere of 6% CO_2 at 37 °C, 50 ul of Bright-Glo (Promega) was added to each well. Luciferase activity was measured by using L-Max luminometer (Molecular Device). The amount of luciferase activity induced by treatment with NDP- -MSH was defined as 100% to obtain the relative efficacy of test compounds. The $EC_{0.5\ MSH}$ was defined as the concentration of test compounds that results in half maximal activity of NDP- -MSH. The EC_{50} was defined as the concentration of test compound that results in half maximal activity of its own.

2. cAMP Accumulation Assay.

The membrane fraction cAMP assay was used to identify MC4R agonist compounds.

Cell lines expressing human melanocortin receptor 4 (MC4R) were grown in Φ150 mm culture dishes in DMEM (GIBCO-BRL) supplemented with 10% FBS, 200 ug/ml Geneticin (GIBCO-BRL), and antibiotics (penicillin and streptomycin) (GIBCO-BRL) in an atmosphere of 6% CO_2 at 37 °C. When the cells were fully grown, the cells were washed once with 10 ml of Ca^{++}, Mg^{++} free DPBS. The cells were incubated with 8 ml of Ca^{++}, Mg^{++} free DPBS for 15 – 30 min at 37 °C until the cells were easily detached by triturating with pipette. The cells were harvested into 50 ml of conical tubes, and spun at 1500 rpm for 5 min. The supernatant was discarded, and

the cells were resuspended in 8 ml of Ca^{++}, Mg^{++} free DPBS, and spun at 1500 rpm for 5 min. The supernatant was discarded, and the pellets were resuspended in 3 ml of membrane preparation buffer (10mM Tris pH 7.4; 0.32M sucrose; 4ug/ml leupeptin; 10uM phosphoramidon; 40ug/ml bacitracin; 5ug/ml aprotinin). The pellets were homogenized with dounce homogenizer (Bellco with type "B" glass pestle) using 20 strokes. The homogenate was centrifuged at 1300Xg at 4°C for 10 min. The supernatants were collected, and the pellets were resuspended in membrane preparation buffer, and homogenization and centrifugation were repeated. All of the supernatants were collected and centrifuged at 40,000 rpm (Beckman XL-100K Ultracentrifuge, Rotor 45 Ti, 50 ml centrifuge tube) at 4°C for 15 min. The pellets were resuspended in membrane preparation buffer, and protein was determined by BCA assay kit (PIERCE). Aliquots were placed in tubes and stored at - 80 ° C.

20 ul of NDP- -MSH or test compounds diluted in DMSO were added onto each well of 96well V-plate. 20 ul of 750ug/ml membrane fraction in MP buffer was added onto each well. After the reaction was performed at rt for 15 min, cAMP was measured using cAMP (^3H) assay Kit (Amersham, cat. No. TRK 432). The amount of cAMP produced by the treatment with test compound was compared to that produced in the response to NDP- -MSH which was defined as 100% agonist. The EC_{50} was defined as the concentration of test compound that results in half maximal activity of its own.

As can be seen from the above results, the compounds according to the present invention showed agonistic efficacy and binding affinity to each MCR. In particular, the compounds according to the present invention showed excellent agonistic efficacy and binding affinity to the MCR4. i.e., 0.005 μM – 10 μM of EC_{50} value and 0.01 μM – 50 μM of IC_{50} value. For example, the compounds of examples 1, 2 and 3 showed 0.005 μM – 0.5 μM of EC_{50} value, and 0.1 μM – 0.5 μM of IC_{50} value, against MCR4.

C. In vivo food intake models

1. Hypophasic effects in fasted mice

Hypophasic effects of melanocortinergic ligands are determined by using the food-deprived mouse model (male ddY mice). The animals are individually housed. One day before treatment, the animals are grouped (7-10 animals/group), based on their

basal daily food intakes, and then their food is removed for 20 h fasting before treatment. In the morning of the test day, each animal receives the administration of vehicle or test substance via oral gavage, and 1 h after, food is re-supplied. Food intakes after the food-supply are measured for the first 1 h period.

2. Effects on nocturnal food intake

Effects on nocturnal food intake are determined in male ICR mice. The animals are housed individually, and are grouped (7-10 animals/group) based on their basal daily food intakes. Each animal receives the administration of vehicle or test substance via oral gavage 1 h before starting the dark phase, and food is removed. Food is resupplied 1h after the administration, and food intakes are measured at 1, 2, 4, 8, 24 h after the food is supplied.

3. Effects on food intake and body weight change in ob/ob mice

Effects on food intake and body weight change are determined in male 8 wks old ob/ob mice. The animals are housed individually, and are grouped (7-10 animals/group) based on their basal body weights. Each animal receives the administration of vehicle or test substance via oral gavage once a day for 14 days. Food intakes and body weigh changes are measured daily.

4. Effects on food intake and body weight change in diet-induced obese (DIO) mice

Effects on food intake and body weight change are determined in male DIO mice. The DIO mice are prepared by feeding C57BL/6 mice on high fat diet for more than 8 weeks. The DIO animals are housed individually, and are grouped (7-10 animals/group) based on their basal body weights. Each animal receives the administration of vehicle or test substance via oral gavage once a day for 14 days. Food intakes and body weigh changes are measured daily.

D. Anti-inflammatory effects in an acute inflammation model

Anti-inflammatory effects are determined as the effects on crystal-induced Polymorphonuclear Neutrophil (PMN) recruitment. Each Balb/c mouse receives the administration of vehicle or test substance via oral gavage. One hour after the vehicle or drug treatment, the animals receive 3 mg of mono-sodium urea crystals in 0.5 ml of PBS (pH 7.4) buffer (time = 0) by the intraperitoneal injection. At 6 hs after the crystal injection, the animals are euthanized by CO_2 exposure, and then their peritoneal cavities are washed with 3 ml of PBS buffer. Aliquots of the lavage fluids are stained

with Turk's solution (0.01% crystal violet in 3% acetic acid), and the number of cells are counted by using a hemacytometer and a light microscope. PMNs are counted as many as (1 ~ 10) x 10^6 per mouse. Data are presented as 10^6 PMN per mouse.

E. Erectile effects

The erectile effect of the test substance is determined by counting the number of erection of male Sprague Dawley rats. Each animal receives the administration of vehicle or test substance via oral gavage 30 min before the test session, and then is placed in a 2-liter glass beaker. The beakers are located on an observation box designed for the ventral view of the animals. The number of erection is counted by observing the posture of the animals (hip constriction, hip thust, tiptoe posture) for 1 h.